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(54) Improvements in or relating to benzimidazoles.

(57) Certain N-substituted benzimidazoles, which are potent antiviral agents, are disclosed. The compounds are prepared by reacting the corresponding keto derivative with an alkylating agent or by cyclizing the corresponding *o*-phenylenediamine. Pharmaceutical formulations containing such compounds and a method of treating viral infections are provided.

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IMPROVEMENTS IN OR RELATING TO BENZIMIDAZOLES

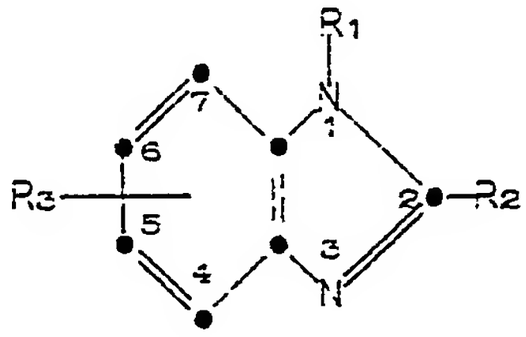
The incidence of viral upper respiratory disease is immense. It has been estimated that nearly a billion cases annually appear in the United States alone. Studies performed in England [Tyrell and Bynoe, Lancet 1, 76 (1966)] indicated that 74 percent of persons having colds were infected with rhinoviruses. Because more than 80 strains of rhinoviruses are already identified, the development of a practical rhinovirus vaccine is not feasible, and chemotherapy appears to be the more desirable approach.

The ability of chemical compounds to suppress the growth of viruses in vitro is readily demonstrated by using a virus plaque suppression test similar to that described by Siminoff, Applied Microbiology, 9(1), 66 (1961).

Certain benzimidazole compounds have been found to possess anti-viral activity, including those compounds found in the following U.S. Patents: 4,150,028, 4,216,313, 4,293,558, and 4,338,315 (1-thiazolinyl and -thiazinyl keto benzimidazoles); 4,174,454 (alkylidenylmethyl-substituted-1-sulfonylbenzimidazoles); 4,018,790, 4,118,573, 4,196,125, 4,243,813 and 4,316,021 (1-sulfonyl-2,5(6)-substituted benzimidazoles); 4,008,243 (1-thiazolinyl and -thiazinyl benzimidazole esters); 4,230,868 (α-alkyl-α-hydroxybenzyl-substituted-1-sulfonylbenzimidazoles); and 4,118,742, 4,289,782, and 4,338,329 (carbonyl substituted-1-sulfonylbenzimidazoles).

This invention is directed to novel benzimidazole compounds which inhibit the growth of viruses, particularly rhinoviruses, polio viruses, Coxsackie viruses, echo virus, and Mengo virus.

This invention concerns pharmacologically useful benzimidazole compounds having the formula



(I)

wherein:

R_1 is C_1-C_8 alkyl, C_2-C_8 alkenyl, C_3-C_7 cycloalkyl, C_5-C_7 cycloalken-1-yl, 2-pyridyl, 2-thiazolyl, adamantyl, hydroxy-substituted C_1-C_8 alkyl, unsubstituted or substituted phenyl, unsubstituted or substituted benzyl, or $R_4R_5NCH_2$- , where R_4 and R_5 are independently C_1-C_3 alkyl or R_4 and R_5, when taken together with the nitrogen atom to which they are attached, are pyrrolidino, piperidino, or morpholino;

R_2 is hydrogen, amino, C_1-C_4 alkylamino, methylmercapto, hydroxy, C_1-C_4 acylamino, or 1-hydroxyethyl;

R_3 is C_2-C_8 alkanoyloxy, unsubstituted or substituted phenylacetoxy, unsubstituted or substituted benzoyloxy, or $R_6\overset{\overset{Z}{\|}}{C}$- ;

Z is oxygen, hydroxyimino, C_1-C_4 alkoxyimino, C_1-C_4 acyloxyimino, hydrazono, C_1-C_7 alkylidene, =CHBr, =CHCl, =CBr_2, =CCl_2, =CBrCl, =CHCN, =$CHCONH_2$, or =$CHCO_2$(C_1-C_4 alkyl);

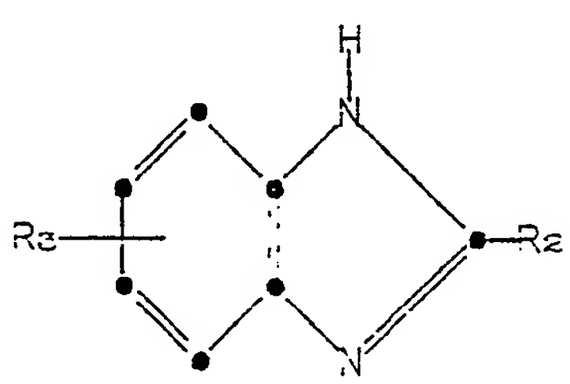
R_6 is C_1-C_7 alkyl, C_3-C_7 cycloalkyl, (C_3-C_7 cycloalkyl)methyl, 2-(C_3-C_7 cycloalkyl)ethyl, unsubstituted or substituted benzyl, unsubstituted or substituted phenyl; and

R_3 is at the 5 or 6 position,

subject to the limitation that when R_2 is hydroxy, R_1 may only be C_5-C_7 1-cycloalkenyl; and pharmaceutically acceptable salts thereof.

The compounds of formula I are prepared by a process which comprises:

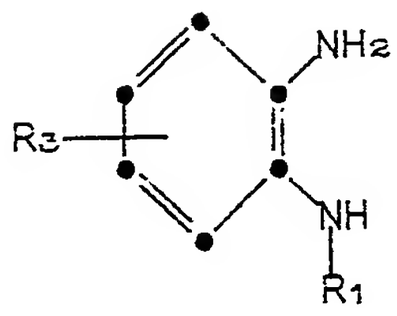
(A) alkylating a benzimidazole compound of the formula



(II)

wherein R_3 is defined as above and R_2 is other than hydroxy or amino, with a compound of the formula R_1X where R_1 is defined as above and X is fluoro, chloro, bromo, or iodo, to provide the compounds of formula I where R_2 is other than hydroxy or amino; or

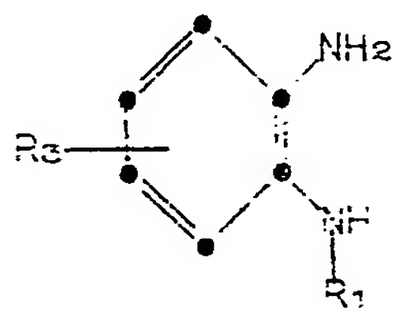
(B) heating a compound of the formula



(V)

wherein R_1 and R_3 are defined as above, with formic acid or lactic acid, preferably in the presence of a mineral acid, to provide the compounds of formula I wherein R_2 is hydrogen or 1-hydroxyethyl; or

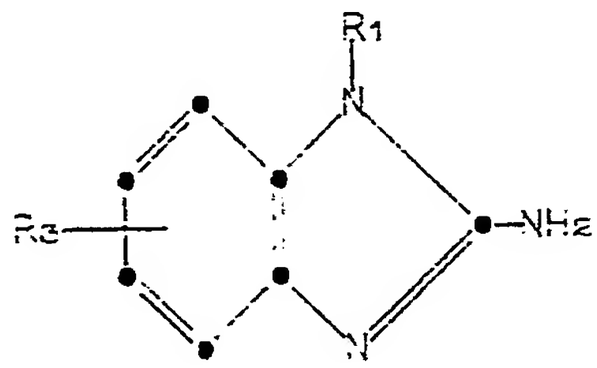
(C) cyclizing a compound of the formula



(V)

wherein R_1 and R_3 are defined as above, with cyanogen halide, to provide the compounds of formula I wherein R_2 is amino; or

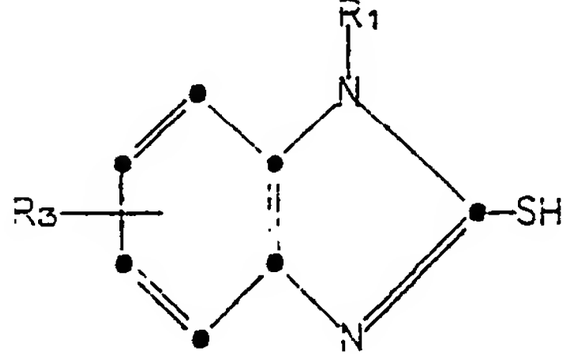
(D) alkylating a benzimidazole compound of the formula



(IB)

wherein R_1 and R_3 are defined as above, with a C_1-C_4 alkyl halide, to provide the compounds of formula I wherein R_2 is C_1-C_4 alkylamino; or

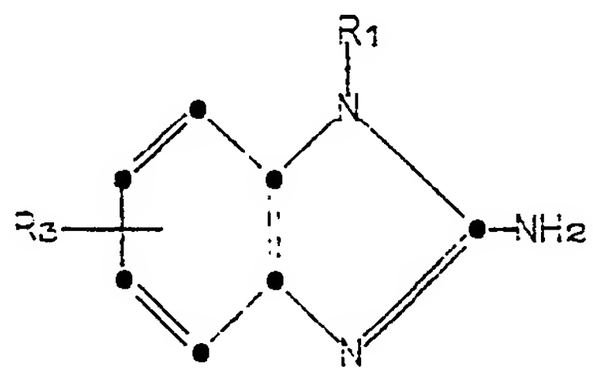
(E) alkylating a benzimidazole compound of the formula



(IC)

wherein R_1 and R_3 are defined as above, with methyl halide in the presence of a weak base, to provide the compounds of formula I wherein R_2 is methylmercapto; or

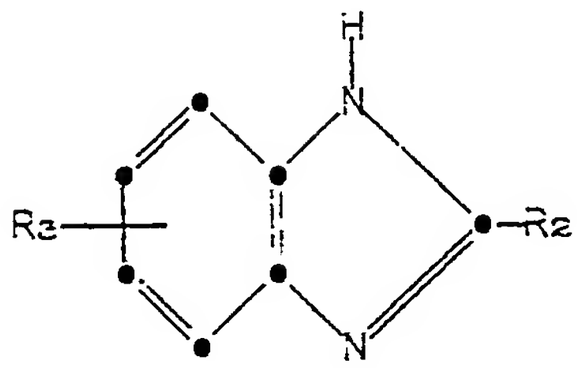
(F) acylating a benzimidazole compound of the formula



(IB)

wherein R_1 and R_3 are defined as above, with a C_2-C_4 anhydride, a mixed anhydride of formic and acetic anhydride, or a C_1-C_4 acyl halide, to provide the compounds of formula I wherein R_2 is C_1-C_4 acylamino; or

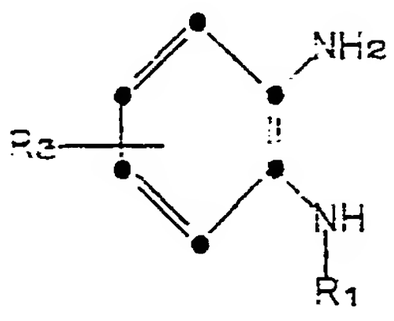
(G) reacting a benzimidazole compound of the formula



(II)

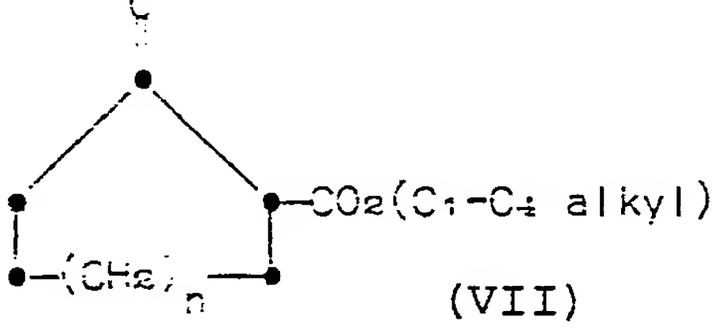
wherein R_2 and R_3 are defined as above, with R_4R_5NH, where R_4 and R_5 are defined as above, and formaldehyde, to provide the compounds of formula I wherein R_1 is $R_4R_5NCH_2-$; or

(H) condensing a compound of the formula



(V)

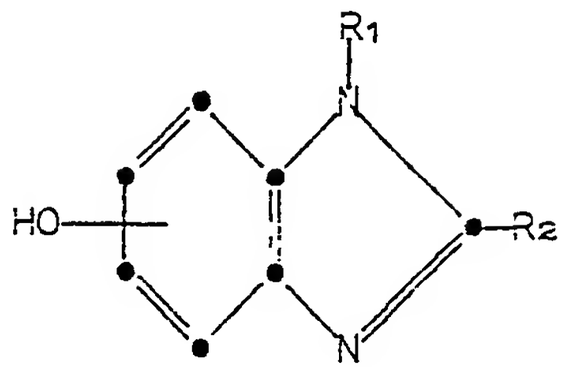
wherein R_1 and R_3 are defined as above, with a β-keto ester of the formula



(VII)

wherein n is 0-2, to provide the compounds of formula I wherein R_2 is hydrogen and R_1 is C_5-C_7 cycloalken-1-yl; or

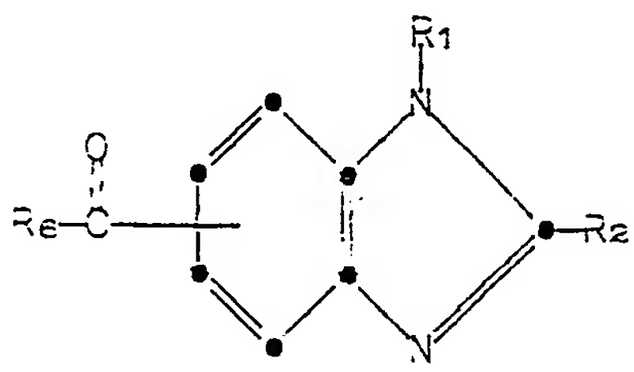
(I) esterifying a benzimidazole compound of the formula



(ID)

wherein R_1 is defined as above, and R_2 does not contain a hydroxy group, with an anhydride or acyl halide, to provide the compounds of formula I wherein R_3 is C_2-C_8 alkanoyloxy, unsubstituted or substituted phenylacetoxy, or unsubstituted or substituted benzoyloxy; or

(J) reacting a benzimidazole compound of the formula



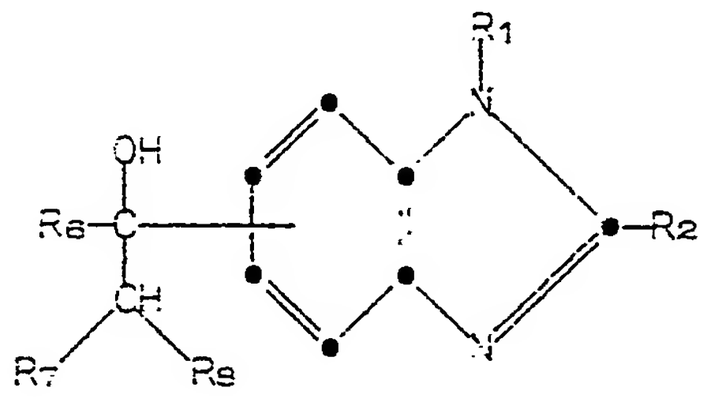
(IA)

wherein R_1, R_2 and R_6 are defined as above, with hydroxylamine, or its hydrochloride salt, hydrazine or C_1-C_4 alkoxyamine, to provide the compounds of formula I wherein Z is hydroxyimino, hydrazono, or C_1-C_4 alkoxyimino; or

(K) acylating a compound of formula I wherein Z is hydroxyimino with a C_1-C_4 anhydride or a C_1-C_4 acyl halide, to provide the compounds of formula I wherein Z is C_1-C_4 acyloxyimino; or

(L) etherifying a compound of formula I wherein Z is hydroxyimino with a C_1-C_4 alkyl halide, or alkylating the compound of formula I where R_3 is R_6-C(=O)- with a C_1-C_4 alkoxyamine, to provide the compounds of formula I wherein Z is C_1-C_4 alkoxyimino; or

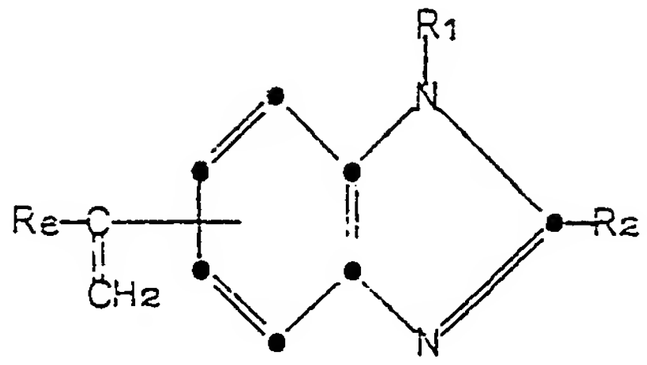
(M) dehydrating a benzimidazole compound of the formula



(IF)

wherein R_1, R_2 and R_6 are defined as above, and one of R_7 and R_8 is hydrogen and the other of R_7 and R_8 is hydrogen, C_1-C_6 alkyl, -CN, $-CONH_2$, or $-CO_2-(C_1-C_4$ alkyl), with an acid, to provide the compounds of formula I wherein Z is C_1-C_7 alkylidene, =CHCN, $=CHCONH_2$, or $=CHCO_2(C_1-C_4$ alkyl); or

(N) reacting a benzimidazole compound of the formula



(IGc)

wherein R_1, R_2 and R_6 are defined as above, with a halogenating agent, to provide the compounds of formula I wherein Z is =CHBr, =CHCl, =CBr_2, =CCl_2, or =CBrCl; or

(O) resolving the benzimidazole compounds of formula I into its 5 and 6 isomers; or

(P) resolving the benzimidazole compounds of formula I wherein Z is hydroxyimino, C_1-C_4 alkoxyimino, C_1-C_4 acyloxyimino, or hydrazono into its syn and anti isomers; or

(Q) resolving the benzimidazole compounds of formula I wherein Z is C_1-C_7 alkylidene, =CHBr, =CHCl, =CBr_2, =CCl_2, =CBrCl, =CHCN, =$CHCONH_2$ or =$CHCO_2$(C_1-C_4 alkyl) into its cis and trans isomers; or

(R) salifying the compounds of formula I to form pharmaceutically acceptable salts.

This invention additionally provides a method for controlling the growth of viruses which comprises administering to a warm-blooded mammal an effective antiviral amount of a benzimidazole derivative of formula I, or a pharmaceutically acceptable salt thereof.

A further embodiment of the present invention includes a pharmaceutical formulation comprising as an active ingredient a benzimidazole derivative of formula I,

or a pharmaceutically acceptable acid addition salt thereof, associated with one or more pharmaceutically acceptable carriers.

The present invention relates to new benzimidazole compounds of formula I that are potent antiviral agents and that are accordingly useful in the treatment and control of viral growth, including growth attributable to rhinovirus, polio, coxsackie, echo virus, mengo virus, influenza, and related viral growths.

A preferred group of compounds are the compounds of formula (I) wherein:

R_1 is C_1-C_8 alkyl, C_2-C_8 alkenyl, phenyl, substituted phenyl, or C_3-C_7 cycloalkyl;

R_2 is hydrogen or amino; and

R_3 is $R_6C(=Z)$- wherein R_6 is phenyl or substituted phenyl.

Especially preferred compounds of formula (I) are those wherein:

R_1 is isopropyl, cyclohexyl or phenyl;

R_2 is hydrogen or amino; and

R_3 is $R_6C(=Z)$- wherein R_6 is phenyl and Z is oxygen, hydroxyimino, =CHBr, =CHCN, $=CHCH_3$, or $=CHCONH_2$.

Especially preferred compounds are those of formula I wherein R_3 is at the 6 position.

Illustrative of the compounds provided by formula I are the following:

1-isopropyl-2-amino-5(6)-acetylbenzimidazole,

1-cyclopentyl-2-acetamido-5(6)-propionylbenzimidazole,

1-butyl-2-formamido-5(6)-(1-hydrazonooctyl)-benzimidazole,

1-dimethylaminomethyl-2-methylmercapto-5(6)-[(α-butoxyimino)cycloheptylmethyl]benzimidazole,

1-morpholinylmethyl-5(6)-hydroxybenzimidazole,

1-piperidinylmethyl-2-formamido-5(6)-heptanoyloxybenzimidazole,

1-(N-methyl-N-propylaminomethyl)-2-butylamino-5(6)-(4-chlorobenzoyloxy)benzimidazole,

1-phenyl-2-propionamido-5(6)-[(1-methoxyimino-2-cyclopentyl)ethyl]benzimidazole,

1-(2-thiazolyl)-2-acetamido-5(6)-(3,4-dichlorobenzoyl)benzimidazole,

1-diisopropylaminomethyl-2-(1-hydroxyethyl)-5(6)-[α-pentylidenebenzyl]benzimidazole,

1-cyclobutyl-2-propionamido-5(6)-hydroxy-benzimidazole,

1-octyl-5(6)-phenylacetoxybenzimidazole,

1-piperidinylmethyl-2-methylmercapto-5(6)-(α-ethoxyiminocyclopentylmethyl)benzimidazole,

1-pentyl-2-acetamido-5(6)-heptanoylbenzimidazole,

1-(1-cyclopentenyl)-2-hydroxy-5(6)-(α-hydrazonocyclopentylmethyl)benzimidazole,

1-cyclohexyl-2-amino-5(6)-(4-methoxybenzoyl-oxy)benzimidazole,

1-(4-methoxyphenyl)-5(6)-(α-hexylidenebenzyl)-benzimidazole,

1-(1-adamantyl)-2-formamido-5(6)-(3-cyclo-pentylpropionyl)benzimidazole,

1-diethylaminomethyl-2-acetamido-5(6)-(1-ethoxyiminohexyl)benzimidazole,

1-ethyl-2-ethylamino-5(6)-[1-(4-fluorophenyl)-2-cyanoethenyl]benzimidazole,

1-(N-ethyl-N-propylaminomethyl)-2-methylmercapto-5(6)-(α-n-butanoyloxyiminobenzyl)benzimidazole,

1-(morpholinylmethyl-2-(1-hydroxyethyl)-5(6)-(1-phenyl-2-bromoethenyl)benzimidazole,

1-allyl-2-isopropylamino-5(6)-[1-(2,4,6-trimethylphenyl)heptylenyl]benzimidazole,

1-dipropylaminomethyl-2-acetamido-5(6)-(4-trifluoromethylbenzoyl)benzimidazcle,

1-isopropyl-5(6)-(α-methoxyimino-3,4-dichlorobenzyl)benzimidazole,

1-(N-methyl-N-ethylaminomethyl)-2-amino-5(6)-(α-propoxyimino-2-iodo-4-butoxybenzyl)benzimidazole,

1-(1-cycloheptenyl)-2-hydroxy-5(6)-propionyloxybenzimidazole,

1-methyl-2-methylmercapto-5(6)-(α-hydrazono-3-butoxybenzyl)benzimidazole,

1-cyclopropyl-2-amino-5(6)-(4-butylbenzoyl)-benzimidazole,

1-(2-pyridyl)-5(6)-(3-chloro-4-methoxybenzoyl)-benzimidazole,

1-(2-thiazolyl)-2-ethylamino-5(6)-hydroxy-benzimidazole,

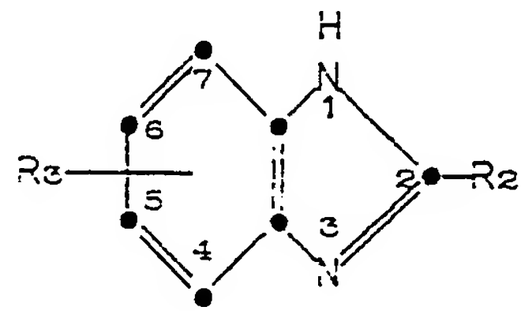
1-t-butyl-2-(1-hydroxyethyl)-5(6)-(α-hydroxy-imino-3-methoxybenzyl)benzimidazole,

1-benzyl-5(6)-(α-hydroxyimino-3-bromo-4-ethoxybenzyl)benzimidazole,

1-(3,5-dimethoxyphenyl)-2-amino-5(6)-pentanoyloxybenzimidazole, and

1-hexyl-2-formamido-5(6)-[(1-hydroxyimino-2-cyclobutyl)ethyl]benzimidazole.

The compounds of formula I are prepared, according to part (A) above, by reacting a tautomeric benzimidazole compound of the formula

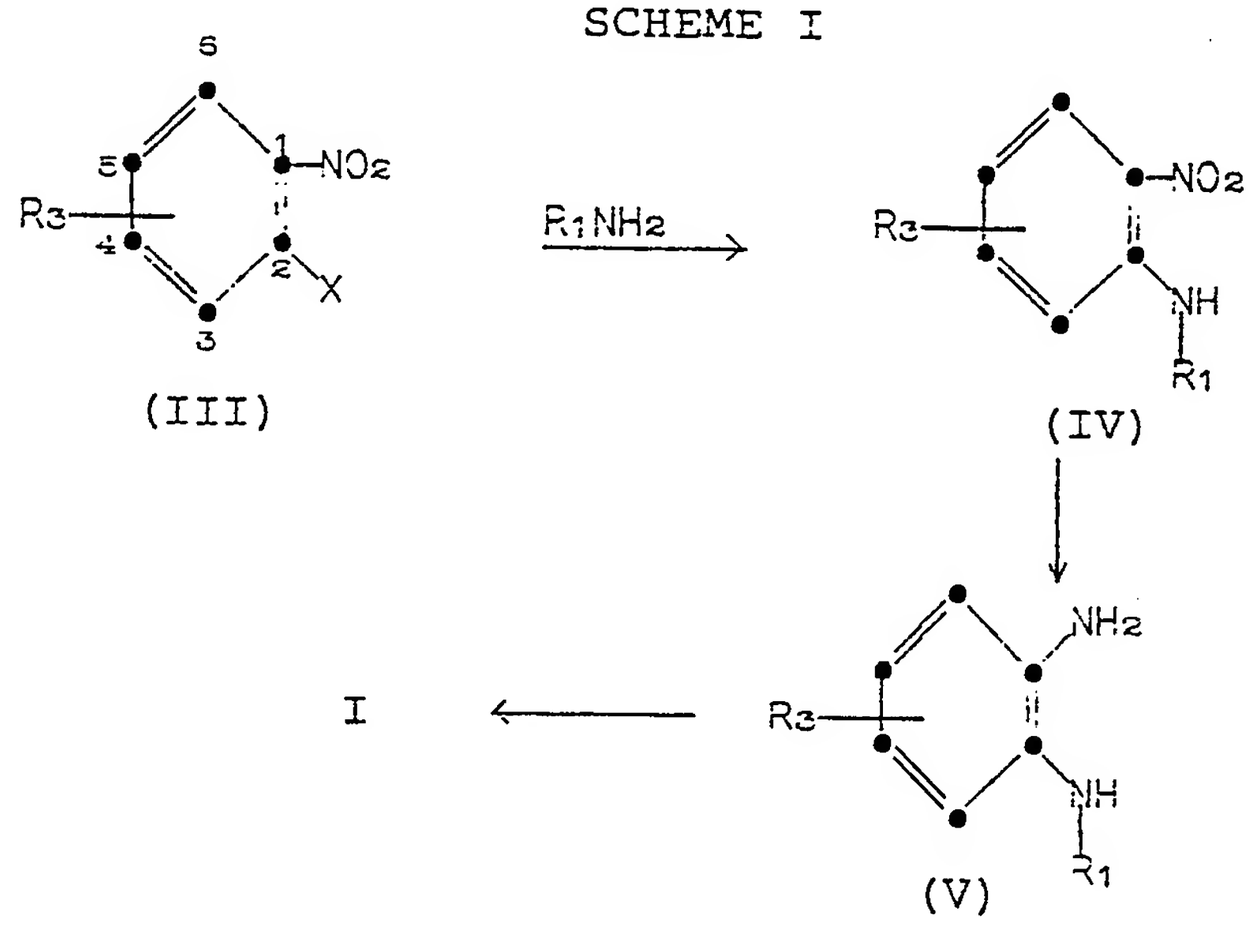


(II)

with a halo compound having the formula R_1X wherein R_1, R_2 and R_3 are as defined hereinabove, and X is fluoro, chloro, bromo, or iodo.

Alternatively, the compounds may be prepared according to the following scheme:

SCHEME I



wherein R_1, R_3, and X are the same as described hereinabove and R_3 is at the 4 or 5 position of III, IV, and V. The last step of Scheme I is shown by part (B), (C) or (H) above.

The term "tautomeric benzimidazole" refers to a benzimidazole reagent which can be substituted at either nitrogen atom with a hydrogen atom. The benzimidazole reactant, unsubstituted on nitrogen and bearing a substituent group at the 5 position of the benzene moiety, has a corresponding tautomeric form wherein the substituent resides alternatively at the 6 position. The isomer mixture can be indicated by numbering the alternate positions as 5(6). As a consequence of such tautomerism, the reaction of a 5(6)-substituted N-unsubstituted benzimidazole with R_1X produces isomeric mixtures of 5(6)-substituted N-substituted benzimidazoles.

The term "C_1-C_8 alkyl" refers to the straight and branched aliphatic radicals of one to eight carbon atoms including methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, amyl, isoamyl, sec-amyl, sec-isoamyl (1,2-dimethylpropyl), tert-amyl (1,1-dimethylpropyl), hexyl, isohexyl, (4-methylpentyl), sec-hexyl (1-methylpentyl), 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 1,2,2-trimethylpropyl, 1,1,2-trimethylpropyl, heptyl, isoheptyl (5-methylhexyl), sec-heptyl (1-methylhexyl), 2,2-dimethylpentyl, 3,3-dimethylpentyl, 4,4-dimethylpentyl, 1,2-dimethylpentyl, 1,3-dimethylpentyl, 1,4-dimethylpentyl, 1,2,3-trimethylbutyl, 1,1,2-trimethylbutyl, 1,1,3-trimethylbutyl, octyl, isooctyl (6-methylheptyl), sec-octyl (1-methylheptyl), tert-octyl (1,1,3,3-tetramethylbutyl), and the like.

The term C_1-C_8 alkyl includes within its definition the terms "C_1-C_3 alkyl," "C_1-C_4 alkyl," "C_1-C_5 alkyl," "C_1-C_6 alkyl", and "C_1-C_7 alkyl."

The term "C_3-C_7 cycloalkyl" refers to the saturated alicyclic rings of three to seven carbon atoms such as cyclopropyl, methylcyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-, 2-, 3- or 4-methylcyclohexyl, cycloheptyl, and the like. The term "(C_3-C_7 cycloalkyl)methyl" refers to a methyl radical substituted with saturated alicyclic rings of three to seven carbon atoms as exemplified in the term "C_3-C_7 cycloalkyl," such as cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cycloheptylmethyl and the like. The term "2-(C_3-C_7 cycloalkyl)ethyl" refers to ethyl radicals substituted on the carbon atom in the 2 position with saturated alicyclic rings of three to seven carbon atoms.

The term "C_5-C_7 cycloalken-1-yl" refers to alicyclic rings of five to seven carbon atoms which have a double bond in the 1-position, such as cyclopenten-1-yl, cyclohexen-1-yl, 2-, 3-, or 4-methylcyclohexen-1-yl, cycloheptен-1-yl, and the like.

The term "C_2-C_8 alkanoyl" refers to the straight and branched aliphatic acyl radicals of two to eight carbon atoms such as acetyl, propionyl, butyryl, 2-methylpropionyl, pentanoyl, hexanoyl, heptanoyl, octanoyl, and the like.

The term "C_1-C_7 alkylidene" refers to straight and branched alkylidene radicals of one to seven carbon atoms such as methylene, ethylidene,

propylidene, isopropylidene, butylidene, isobutylidene, 3-methylbutylidene, n-hexylidene and the like.

The term "C_1-C_4 alkoxy" includes the straight and branched aliphatic ether radicals of one to four carbon atoms such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, and the like. The term "C_1-C_4 alkoxyimino" refers to the O-aliphatic hydroxyimine radical of one to four carbon atoms derived from hydroxylamine. Methoxyamine hydrochloride is available from commercial sources. Other hydroxylamine derivatives are available by alkylation of acetone oxime by C_1-C_4 alkyl halides followed by acid hydrolysis.

The term "substituted" -phenyl, -benzyl, -phenylacetoxy, and -benzoyloxy refers to those groups substituted on the aromatic ring with one to three of C_1-C_4 alkyl, C_1-C_4 alkoxy, fluoro, chloro, bromo, iodo, nitro, amino, or trifluoromethyl. The preferred substituent is that in the 4' or para position of the aromatic ring, especially 4'-methoxy.

In the reaction of a tautomeric benzimidazole II with R_1X, the preferred reactants are benzimidazoles bearing 5(6)-substituents which will not react with R_1X under the reaction conditions. The benzimidazole II and R_1X are normally employed in approximately equimolar quantities, although an excess of either can be used if desired. The reaction can be carried out in any number of unreactive solvents, including acetone, tetrahydrofuran (THF), tertiary amides such as N,N-dimethylformamide (DMF), and chlorinated hydrocarbons

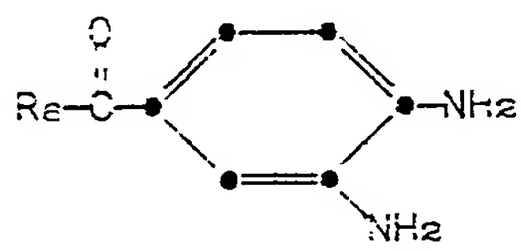
such as dichloromethane, dichloroethane and chloroform. The reaction medium may also contain added base to serve as an acid-binding agent. Some examples of suitable bases for this purpose are pyridine, triethylamine, N-methylmorpholine, sodium bicarbonate, and sodium hydride. A preferred solvent medium for the reaction is DMF containing sodium hydride as a base.

The reaction is best carried out at a temperature between 0°C. and the reflux temperature of the solvent system employed. Preferably, the reaction is carried out at 0°C. to room temperature. In this temperature range, the reaction is substantially complete within 1 to 48 hours.

The product of the reaction is a 1-substituted benzimidazole of formula I, hereinafter called the benzimidazole compound. The product may be isolated by filtering the reaction mixture and concentrating the filtrate to induce crystallization. Alternatively, the reaction mixture can be evaporated to dryness and the residue treated with a suitable solvent such as acetone or methanol to separate and remove any insoluble material. The solution containing the benzimidazole compound is concentrated to crystallize the product or it is evaporated to give a second residue, which is dissolved in methanol, for example. The benzimidazole compound is recovered from the methanol by crystallization. Chromatography over silica gel may also be employed in the purification scheme, either alone or in combination with the above purification steps.

The reaction of the tautomeric benzimidazole II and R_1X generally provides an approximate 1:1 mixture of 5- and 6-substituted benzimidazole compounds. The isomers are separable by fractional crystallization or by chromatography, as shown by part (O) above.

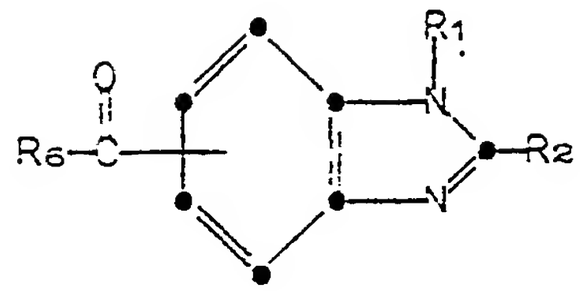
The 5(6)-ketobenzimidazole compounds I wherein R_3 is R_6CO can be prepared from the corresponding 5(6)-ketobenzimidazoles II by reaction with R_1X. The ketobenzimidazole reactant II can be prepared from the appropriate keto o-phenylenediamine by methods known to the benzimidazole art. U.S. Patent No. 3,657,267 discloses the preparation of keto o-phenylenediamines of the formula



(VI)

wherein R_6 is lower alkyl, cycloalkyl, phenyl or phenyl substituted by halogen, lower alkyl or lower alkoxy. The method of preparation involves the ammonolysis and reduction of a 4-halo-3-nitrophenyl ketone which is prepared by the Friedel-Crafts reaction of either (1) a 4-halo-3-nitrobenzoyl chloride with an appropriate hydrocarbon or (2) a halobenzene with an appropriate acid chloride followed by aromatic nitration. Such methods make available the required keto o-phenylenediamines wherein R_6 in the formula above is additionally C_3-C_7 cycloalkyl, (C_3-C_7 cycloalkyl)methyl,

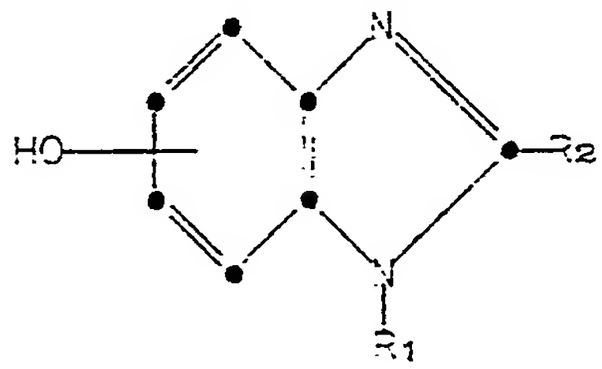
2-(C_3-C_7 cycloalkyl)ethyl or benzyl. Alternatively, the ketobenzimidazole reactants can be prepared from acetanilide by a Friedel-Crafts acylation with the appropriate derivative of a C_2-C_8 alkanoic acid, C_3-C_7 cycloalkyl carboxylic acid, C_3-C_7 cycloalkylacetic acid, 3-(C_3-C_7 cycloalkyl)propionic acid, phenylacetic acid, benzoic acid or substituted benzoic acid. The resulting 4-ketoacetanilide is nitrated to give a 2-nitro-4-ketoacetanilide. The acetanilide is hydrolyzed to give a 2-nitro-4-ketoaniline. The nitroaniline is catalytically hydrogenated to yield a 4-keto-o-phenylenediamine which is ring closed to provide the appropriate 5(6)-ketobenzimidazole. The following embodiment illustrates in principle the preparation of a 5(6)-ketobenzimidazole compound. 4-Propionylacetanilide is nitrated at 0°C. to yield 2-nitro-4-propionylacetanilide. The acetanilide is hydrolyzed and catalytically hydrogenated to give 4-propionyl-o-phenylenediamine. The phenylenediamine is reacted with cyanogen bromide to give 2-amino-5(6)-propionylbenzimidazole. The propionylbenzimidazole is reacted with isopropyl bromide to provide 1-isopropyl-2-amino-5(6)-propionylbenzimidazole. These methods make available the 5(6)-(C_2-C_8)alkanoyl, 5(6)-(C_3-C_7)cycloalkylcarbonyl, 5(6)-(C_3-C_7)cycloalkylacetyl, 5(6)-[3-(C_3-C_7 cycloalkyl)propionyl], 5(6)-phenylacetyl, 5(6)-benzoyl or the 5(6)-substituted-benzoylbenzimidazole compounds. The 5(6)-ketobenzimidazole compounds are represented by the formula



(IA)

wherein R_6 is C_1-C_7 alkyl, C_3-C_7 cycloalkyl, (C_3-C_7 cycloalkyl)methyl, 2-(C_3-C_7 cycloalkyl)ethyl, benzyl, substituted benzyl, phenyl or substituted phenyl, and R_1 and R_2 are as defined previously.

The intermediate benzimidazole compounds wherein R_3 is hydroxy of the formula



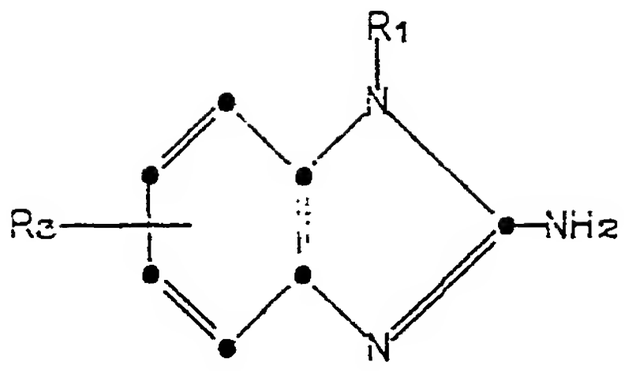
(ID)

wherein R_1 and R_2 are defined as above, can be prepared from the corresponding 5(6)-hydroxybenzimidazole reactants. The preparation of the required hydroxybenzimidazole compounds begins with the reduction of 4-methoxy-2-nitroaniline to the corresponding 4-methoxy-o-phenylenediamine. The phenylenediamine is ring closed to provide a 5(6)-methoxybenzimidazole by methods known to the benzimidazole art. The methyl ether is cleaved with hydrobromic acid to give a 5(6)-hydroxybenzimidazole. The hydroxybenzimidazole is reacted

with the appropriate R_1X to provide the required 1-substituted-5(6)-hydroxybenzimidazole compounds.

The phenolic hydroxyl functionality of the 5(6)-hydroxybenzimidazole compounds can be reacted by part (I) above with the anhydrides or halides, such as chlorides of C_2-C_8 alkanoic acids, phenylacetic acids or benzoic acids in an aprotic solvent to provide the corresponding esters. The ester products derived from the 5(6)-hydroxybenzimidazole reactants are respectively the 5(6)-(C_2-C_8)alkanoyloxy-, 5(6)-phenylacetoxy-, or 5(6)-benzoyloxy-benzimidazole compounds. Alternatively the hydroxybenzimidazole compounds can be esterified with the appropriate acid reactant in the presence of 1,1'-carbonyldiimidazole in dimethylformamide.

The benzimidazole compounds which are required as starting materials in the foregoing process can be prepared according to a variety of methods known to the benzimidazole art. The preparation of a variety of benzimidazoles is well documented in Weissberger's The Chemistry of Heterocyclic Compounds, Imidazole and Its Derivatives, Interscience Publishers Co., New York., 1953. The 2-aminobenzimidazoles of formula I can be prepared by part (C) above by cyclizing the appropriate o-phenylenediamines with cyanogen halide, for example cyanogen bromide, as described by Buttle, et al., Bio. Chem. J., 32, 1101 (1938) and British Pat. 551,524. See also U.S. Patent No. 4,118,742, Example 29(A). Acylation of the 2-aminobenzimidazole reactant of the formula



(IB)

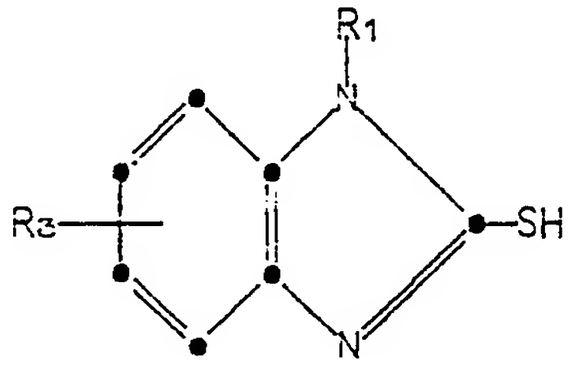
wherein R_1 and R_3 are defined as before, by part (F) above, with acetic, propionic, or butyric anhydride provides the respective 2-acetamido, 2-propionamido, or 2-butyramido benzimidazoles. The 2-formamidobenzimidazole reagents can be obtained by reacting the appropriate 2-aminobenzimidazole with the mixed anhydride obtained from formic acid and acetic anhydride. Alternatively, the 2-acylamino benzimidazole compounds can be prepared from the corresponding 2-aminobenzimidazole compounds by acylation with the appropriate acyl halide as described hereinabove.

The 2-unsubstituted benzimidazoles (I, R_2 is hydrogen) are prepared by heating the appropriate o-phenylenediamine of formula V, by part (B) above, with formic acid, usually in the presence of a mineral acid, such as hydrochloric acid. The 2-(1-hydroxyethyl) substituted benzimidazoles are similarly prepared using lactic acid instead of formic acid.

In the preparation of the preferred compounds where R_6 is phenyl or substituted phenyl, a preferred route of synthesis consists of the Friedel-Crafts acylation of 3,4-dinitrobenzoyl chloride upon the appropriately substituted benzene. The resulting 3,4-

dinitrobenzophenone is then chemically or catalytically reduced to the corresponding 3,4-diaminobenzophenone which is then ring closed in the usual way.

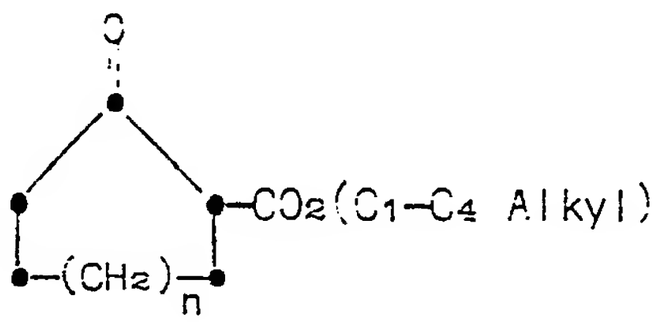
The 2-methylmercaptobenzimidazoles of formula I are prepared by part (E) above, by treating the respective 2-thiobenzimidazole of the formula



(IC)

wherein R_1 and R_3 are defined as above, with methylhalide, e.g. methyliodide, in the presence of a weak base. The 2-thio compounds of formula IC are prepared by heating the appropriate o-phenylenediamine with potassium ethyl xanthate in the usual manner.

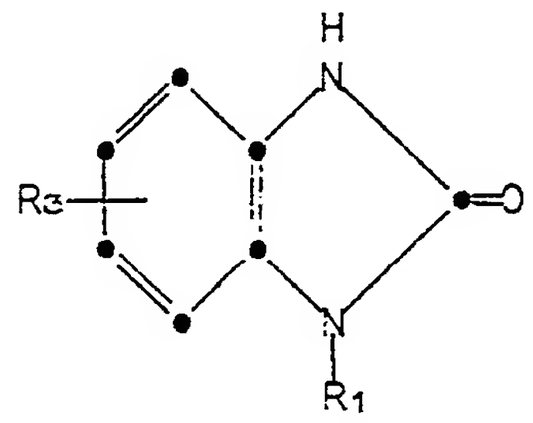
The compounds of formula I wherein R_2 is hydroxy are prepared by condensing the appropriate o-phenylenediamine of formula V, by part (H) above, with a β-keto ester of formula



(VII)

where n is 0-2, according to the method summarized in Chemical Reviews, 74 (3), 384 (1974), resulting both in ring closure to the 2-hydroxy benzimidazole and substi-

tution on the nitrogen atom with a C_5-C_7 cycloalken-1-yl substituent. Both 5- and 6-isomers are formed. The 2-hydroxy benzimidazole exists with its tautomer represented by the formula



(IE)

Additionally, N-substituted 5(6)-benzimidazoles may be prepared by the reaction of R_1X with the appropriate o-phenylenediamine followed by ring closure in the usual manner.

All of the above procedures result in the preparation of isomeric mixtures of the 5- and 6-substituted benzimidazoles of formula I. The mixture may be separated into the individual isomers, by part (O) above, if desired, by chromatography and/or by fractional crystallization. Since the 6-isomer is usually preferred, a regiospecific synthesis is desirable to eliminate the extra purification steps and loss of half of the material as the undesired isomer. Such a procedure is outlined in Scheme I, hereinabove.

The o-nitrohalobenzene derivative III is reacted with R_1NH_2 at a temperature of 100-200°C. to provide the corresponding aniline IV. For a volatile amine, the general procedure involves the reaction of the amine in a solvent, such as methanol, and heating

in a stainless steel autoclave at about 140-150°C. for about 16 hours. For non-volatile or aromatic amines, equal equivalents of III and R_1NH_2 are heated with anhydrous sodium carbonate in a high boiling non-reactive solvent, such as sulfolane. Heating for 3-4 hours at 100-200°C. is usually adequate to give good yields of IV. When aromatic amines are used, a temperature range of 180-200°C. is preferred.

The aniline IV is converted to diamine V by the usual methods of chemical or catalytic reduction. Preferably, the reduction is done through catalytic hydrogenation, in a non-reactive solvent such tetrahydrofuran, in the presence of a catalyst, such as Raney nickel.

The diamine V is then ring closed to the desired benzimidazole I in the manner previously described giving the single 5- or 6-isomer.

The required starting materials above, including R_1X, R_1NH_2, and III, are either commercially available or may be prepared by methods known in the literature. In the preferred case wherein R_3 is $Z=C(R_6)-$ and R_6 is a phenyl derivative, the preferred method of preparing compounds of formula III is the condensation of a phenyl acetonitrile with o-nitrochlorobenzene to give the intermediate 4-(phenylcyanomethylene)-2-chlorocyclohexa-2,5-diene-1-one oxime which upon oxidation with basic hydrogen peroxide gives III (X is chloro). The latter sequence was reported by Davis et al., J. Org. Chem., 26, 4270 (1961) and Davis et al., J. Am. Chem. Soc., 82, 2913 (1960).

Dialkylaminomethyl substituents can be introduced into the benzimidazoles, by part (G) above, by means of the Mannich reaction. The N-unsubstituted benzimidazole is allowed to react with the appropriate dialkylamine in the presence of formaldehyde to produce the desired N-(dialkylaminomethyl) derivatives of formula I. If such derivatives are desired, the reaction is usually performed at the end of the synthesis because subsequent reaction steps, such as oxime formation, may remove the dialkylaminomethyl functionality.

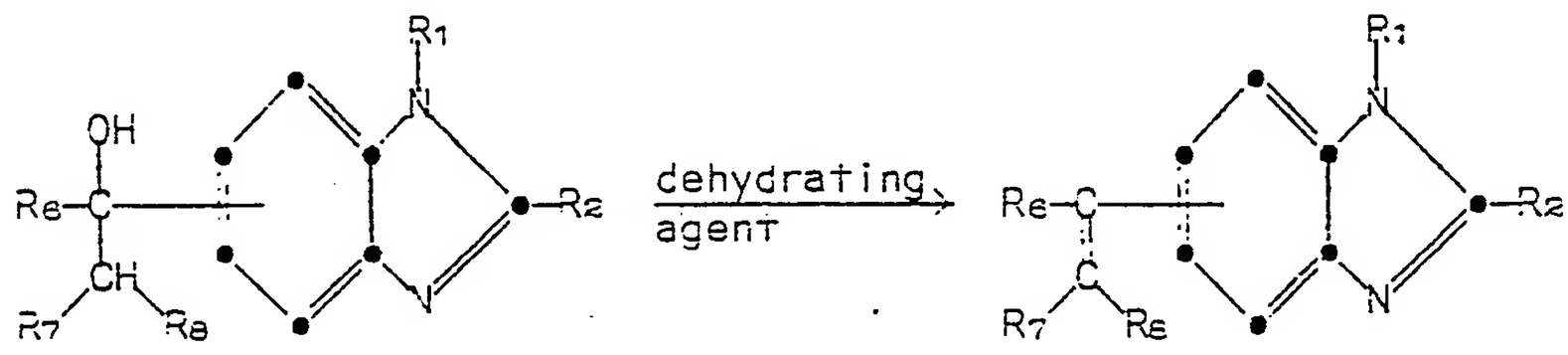
Hydroxyimino derivatives can be prepared from the corresponding keto compounds of formula IA, by part (J) above, by treatment with hydroxylamine in the usual manner. Similarly, the hydrazono derivatives can be prepared from the keto compounds by reacting with hydrazine.

The compounds of formula I, wherein R_3 is $Z=C(R_6)-$ and Z is an acyloxyimine, are prepared, by part (K) above, by reacting the corresponding hydroxyiminobenzimidazole with the appropriate acylating agent (such as an anhydride or acyl halide).

The compounds of formula I wherein R_3 is $Z=C(R_6)-$ and Z is an alkoxyimine are prepared, by part (L) above, by reacting the appropriate ketobenzimidazole of formula IA with an alkoxyamine, or by alkylating the corresponding hydroxyiminobenzimidazole (suitable alkylating agents are an alkali metal alkoxide and alkyl halide).

When the oximes and oxime derivatives are prepared, the products are usually mixtures of the syn and anti isomers. The proportion of the anti isomer can be increased by conventional methods, part (P) above, e.g. fractional crystallization or high pressure chromatography. As the anti isomer is usually more active biologically, this enrichment process is useful.

The compounds of formula I wherein R_3 is $Z=C(R_6)-$ and Z is C_1-C_7 alkylidene, $=CHCN$, $=CHCONH_2$, and $=CHCO_2(C_1-C_4$ alkyl) are formed by the dehydration of the corresponding carbinol, see part (M) above. Such dehydration reaction of a benzimidazole carbinol is depicted by the following generalized scheme:



(IF) (IG)

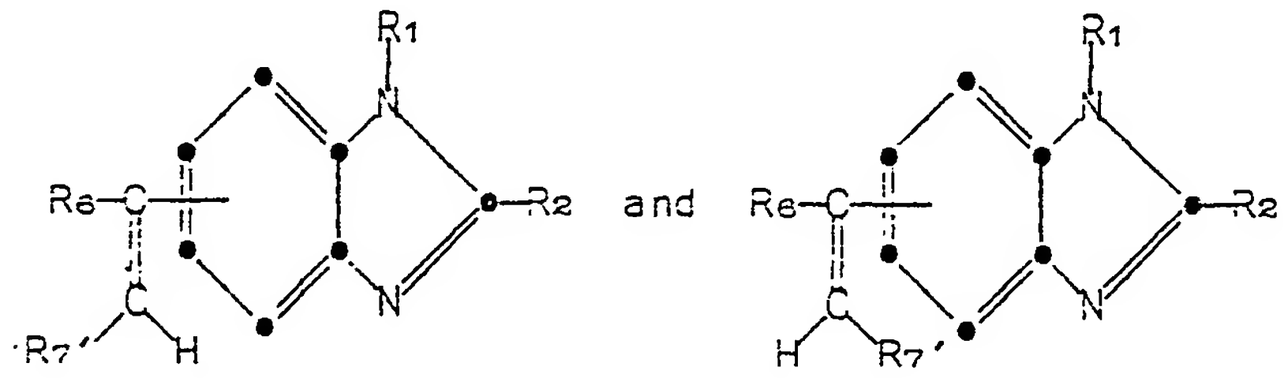
wherein R_1, R_2 and R_6 have the above-defined meanings, one of R_7 and R_8 is hydrogen and the other of R_7 and R_8 is hydrogen, C_1-C_6 alkyl, $-CN$, $-CONH_2$, or $-CO_2-(C_1-C_4$ alkyl).

The dehydration of a benzimidazole carbinol according to the above scheme is accomplished by reaction of the carbinol with any of a number of dehydrating agents which are capable of removing a mole of water from each mole of carbinol to thus provide the corresponding olefinic benzimidazole of formula I.

Typical dehydrating agents commonly used include acids such as sulfuric acid, hydrochloric acid, formic acid, polyphosphoric acid and p-toluenesulfonic acid. In a routine dehydration reaction, a carbinol is combined with about an equal weight amount or an excess of a dehydrating agent. The reaction normally is carried out in an organic solvent such as formic acid, chloroform, benzene, dichloromethane, or the like, at a temperature of about 20°C. to the reflux temperature of the particular solvent utilized for the reaction. Under these conditions, the dehydration typically is substantially complete within about one to about forty-eight hours. Longer reaction periods may be employed if desired. The reaction takes place in approximately two hours when the preferred conditions of refluxing formic acid are employed. Upon completion of the dehydration reaction, the product, an olefinic benzimidazole of formula I, can be isolated by simply washing the reaction mixture with a base, for instance dilute aqueous sodium bicarbonate or the like, and removing the organic reaction solvent by evaporation. The product can be further purified if desired by normal methods, including chromatography and crystallization from solvents such as ethanol, ethyl acetate, acetone, and the like.

It should be noted that when R_7 and R_8 in the above general formula IG defining the olefinic benzimidazoles are different, the compounds exist as cis (or Z) and trans (or E) isomers. The dehydration reaction described above generally provides a mixture

of such isomers. For example, dehydration of a compound such as 1-isopropyl-2-amino-5-(α-hydroxy-α-cyanomethylbenzyl)benzimidazole affords a mixture of cis-1-isopropyl-2-amino-5-(α-cyanomethylenebenzyl)-benzimidazole, and the corresponding trans isomer. The cis and trans isomers of the benzimidazoles provided herein are represented by the general formulas:



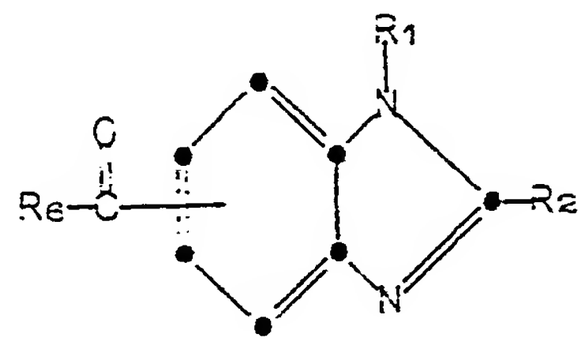
trans (or E) isomer and cis (or Z) isomer

IGa IGb

wherein R_1, R_2, and R_6 are as described hereinabove, and R_7' is the same as R_7 (or R_8) but not hydrogen. Since both the cis and the trans olefinic benzimidazoles of formula I are potent antiviral agents, they can be utilized in the treatment of viral infections either alone or as a mixture.

Isolation of pure cis and pure trans olefinic benzimidazoles of formula I generally is accomplished, by part (Q) above, by chromatography or by crystallization or fractional crystallization from solvents such as methanol, ethanol, acetone, or the like. The trans isomers usually appear more active than the cis compounds, and therefore are preferred over the cis isomers.

The benzimidazole carbinols which are the required starting materials in the above-described dehydration reaction are themselves antiviral agents. Some of the carbinols are prepared by reaction of a 5- or 6-carbonyl substituted benzimidazole with a suitably substituted carbanion. For example, a carbanion of the formula $R_7''CH_2^{\ominus}$ reacts with a ketobenzimidazole of the formula



(IA)

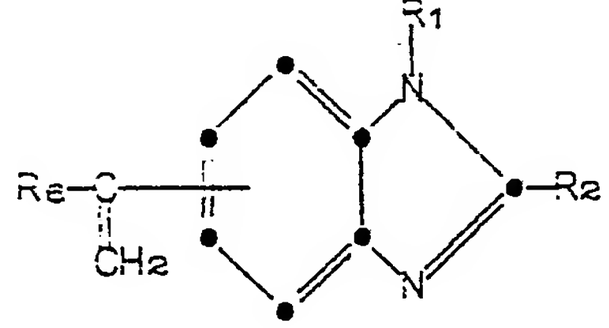
wherein R_1, R_2, and R_6 are the same as described herein above and R_7'' is -CN, $-CONH_2$, or $-CO_2(C_1-C_4$ alkyl) to form the corresponding benzimidazole carbinol. The ketobenzimidazoles are available by the methods described previously. The requisite carbanions are formed by reaction of an active methylene compound with a strong base such as methyl lithium, sodium hydride, n-butyl lithium, lithium diisopropylamide, potassium tert-butoxide, and the like. Active methylene compounds are those which have an electronegative functional group attached to a methyl or methylene group. Typical active methylene compounds which readily form carbanions include compounds of the formulas CH_3CN, CH_3CONH_2, and $CH_3CO_2(C_1-C_4$ alkyl). Protected forms of the active methylene compounds can also be employed; for instance, bis(trimethylsilyl)acetamide may be used

in place of acetamide. Such compounds generally are reacted with about an equimolar quantity or an excess of strong base in an unreactive organic solvent such as diethyl ether, tetrahydrofuran, dimethylformamide, dioxane, diglyme, and the like. For example, an active methylene compound such as ethyl acetate can be reacted with a strong base such as n-butyl lithium in a solvent such as diethyl ether to form the corresponding carbanion, namely lithium ethoxycarbonylcarbanion. Such reactions typically are carried out at a temperature of about -78 to about -50°C., and are substantially complete within about one to about six hours.

Once the carbanion has formed, it typically is not isolated, but rather is reacted *in situ* with a ketobenzimidazole derivative. The carbanion generally is utilized in an excess of about 1 to about 10 molar compared to the ketobenzimidazole, and the reaction is routinely carried out at a temperature of about -70 to about 30°C. The product of the reaction is the aforementioned carbinol benzimidazole, and can be isolated by simply acidifying the reaction mixture, for example with hydrochloric acid, and then removing the reaction solvent, for instance by evaporation under reduced pressure. Further purification of the carbinol benzimidazole generally is not needed, but if desired can be accomplished by routine procedures such as chromatography, crystallization, and the like.

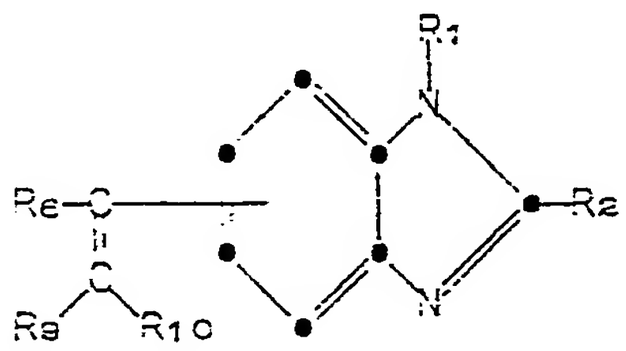
The (α-hydroxy-α-C_1-C_7 alkyl) derivatives are prepared by reacting the corresponding keto derivative with the appropriate Grignard reagent followed by hydrolysis in the usual manner.

The compounds of formula I wherein R_3 is $Z=C(R_6)-$ and Z is =CHCl and =CHBr can be prepared, by part (N) above, by direct halogenation of a 5- or 6-(α-methylenemethyl)benzimidazole derivative. Such reaction can be depicted by the following general scheme:



(IGc)

- halogenating agent



(IGd)

wherein R_1, R_2 and R_6 are as defined above, one of R_9 and R_{10} is hydrogen and the other of R_9 and R_{10} is chloro or bromo.

The methylenemethyl benzimidazoles of formula IGc which are required as starting materials for the halogenation reaction are prepared by the action of a methyl Grignard reagent on a ketobenzimidazole, followed by dehydration of the resulting carbinol, as discussed previously. The halogenating agents commonly utilized in the halogenation reaction include N-chlorosuccinimide and N-bromosuccinimide.

The halogenation reaction generally is carried out by combining the benzimidazole with the halogenating agent in a suitable unreactive organic solvent such as benzene, tetrahydrofuran, chloroform, toluene, diethyl ether, or related solvents. The use of about an equimolar quantity of halogenating agent effects monohalogenation to give a compound wherein one of R_9 and R_{10} is bromo or chloro and the other is hydrogen. The use of a two molar amount or larger excess of a halogenating agent effects dihalogenation and produces a compound wherein R_9 and R_{10} both are halo, e.g. where R_9 and R_{10} are independently chloro or bromo. The reaction generally is carried out at a temperature of about 20 to about 80°C., and normally is complete within about one to about seventy-two hours at such temperature. The product is isolated by simply cooling the reaction mixture and removing the reaction solvent, for instance by evaporation under reduced pressure. The compounds thus prepared can be further purified if desired by chromatography, crystallization, or the like.

It will be appreciated that advantageous chemical reactions can be performed at optional stages of product synthesis. The benzimidazole reactant can be chemically modified and then reacted with the appropriate R_1X to provide the desired product of formula I. Alternatively, a R_1-substituted benzimidazole intermediate can be prepared and then chemically modified to provide the final product. Suitable benzimidazole reactants are those having substituent groups which can

be converted to the desired 5(6)-substituents either prior to or after reaction with the appropriate R_1X.

The pharmaceutically acceptable acid addition salts of formula I include salts derived from inorganic acids such as hydrochloric acid, nitric acid, phosphoric acid, sulfuric acid, hydrobromic acid, hydroiodic acid, phosphorous acid and the like, as well as salts derived from nontoxic organic acids such as aliphatic mono and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic and alkandioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such pharmaceutically acceptable salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, fluoride, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caprate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandelate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, terephthalate, benzenesulfonate, toluenesulfonate, chlorobenzenesulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, β-hydroxybutyrate, glycollate, malate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, and the like salts. Salts from inorganic acids are preferred, especially the hydrochloride salt.

The benzimidazole compounds of formula I were tested as pure compounds and as isomer mixtures. Both isomers inhibit virus growth, the 6-isomer generally being more active than the 5-isomer against the Polio I virus usually used for ascertaining biological activity.

As already pointed out, an additional embodiment of this invention is a pharmaceutical formulation useful in the treatment and prophylactic control of viral infections in mammals, especially humans. The formulations comprise a benzimidazole of formula I in combination with a pharmaceutical diluent, excipient or carrier therefor. The formulation will contain about 0.5 to about 95% by weight of active ingredient. The compounds of formula I may be formulated for convenient oral administration by being mixed with solid diluents such as lactose, sorbitol, mannitol, starch, including potato starch and corn starch, amylopectin, cellulose derivatives, magnesium stearate, calcium stearate, polyethyleneglycol waxes, polyvinylpyrrolidone, and related diluents and excipients. Such formulations ideally are compressed into tablets for convenient oral administration. Alternatively, the formulations may be encapsulated in gelatin capsules or the like, or may be molded into a tablet suited to sublingual administration. The 2-amino benzimidazole compounds of formula IB are preferably administered by the oral route, while it is preferred that the 2-hydrogen compounds of formula I be administered by other than the oral route.

The compounds of formula I may also be administered rectally, and formulations suited to such administration ideally are prepared in the form of suppositories, which contain a benzimidazole of formula I admixed with a suitable neutral fat base or with a vegetable oil or paraffin oil.

Liquid preparations for oral administration may be prepared in the form of syrups or suspensions. Such formulations will contain about 0.5 to about 20 percent by weight of a compound of formula I, in combination with any of a number of suitable adjuvants such as sugar, ethanol, water, glycerol, propylene glycol and the like.

The benzimidazoles provided by formula I also may be administered parenterally to a mammal suffering from a viral infection or in need of prophylactic treatment. For such administration, solutions may be prepared by dissolving a compound of formula I, particularly as an acid addition salt, in a suitable solvent such as isotonic saline, aqueous glucose, or the like. The solutions will contain from about 0.5 to about 80 percent by weight of a benzimidazole of formula I, preferably about 1 to about 20 percent by weight.

The compounds of formula I may also be formulated as a nasal spray or inhaler. Such formulations will contain ideally about 0.5 to about 10 percent by weight of a benzimidazole. Nasal sprays will generally contain about 0.5 to about 5 percent by weight of active ingredient, and will contain carriers

such as non-ionic polyoxyethylated oils, alcohols such as ethanol, flavor agents such as menthol, and propellants such as polyhalogenated methanes.

A further embodiment of this invention is a benzimidazole derivative of formula I, or a pharmaceutically acceptable salt thereof, for use as an antiviral agent. The method includes treating mammals, including humans, suffering from a viral infection or in need of prophylactic control of viral infections. The method includes treatment of domesticated animals such as swine, cattle, horses, and the like. The method comprises administering to a mammal an antiviral amount of a benzimidazole of formula I. As hereinabove pointed out, the compounds can be suitably formulated for convenient administration by any of several routes, including the oral and parenteral routes. While the particular dosage of active compound may vary depending upon the particular benzimidazole selected, the route of administration, the specific virus to be treated or guarded against, the tolerance of the host, and various other parameters known to the medical community, the general rule is that a benzimidazole of formula I will be administered in an antiviral amount, which generally is a dose of about 0.1 to about 500 mg./kg. of animal body weight. A typical dose of active compound will more preferably be about 0.5 to about 250 mg./kg., and ideally about 1 to about 100 mg./kg. Such dosage can be administered about once each day, or in the case of more severe viral infections, the dosage can be administered from two to three times each day or

more often as required. Such repeated dosing may be especially desirable when a compound is formulated as a nasal spray.

In an effort to more fully illustrate this invention, the following detailed preparations and examples are provided. The examples are illustrative only and are not intended to limit the scope of the invention. The term "m/e" used in characterizing the products refers to the mass-to-charge ratio of ions which appear in the mass spectra of the products. The values which correspond to molecular weights of the major peaks are designated "M^+" with the first listed number being the parent peak. When salts were formed, their yields were approximately quantative to the yields of the free base.

Examples 1 and 2

1-Allyl-5-benzoylbenzimidazole and 1-allyl-6-benzoylbenzimidazole

To a solution of 8.8 g. of 5(6)-benzoylbenzimidazole in 150 ml. of dimethylformamide was added 5 ml. of allyl bromide. Two grams of a 50% sodium hydride suspension in oil were added and the reaction was stirred for about two hours at room temperature. The reaction mixture was poured into 300 ml. of ethyl acetate. The resulting suspension was washed three times with 300 ml. of a saturated sodium chloride solution and the organic layer was then evaporated to dryness, giving the title products as a mixture of the 5- and 6-isomers. Mass spectrum M^+= 262, 185, 157, 105 and 77.

Analysis: $C_{17}H_{14}N_2O$;

Calc.: C, 77.84; H, 5.38; N, 10.68;

Found: C, 77.92; H, 5.22; N, 10.46.

The individual isomers were separated by chromatography over silica gel eluting with 70-80% ethyl acetate/20-30% hexane. In the above example, 1.7 g. of the pure 5-isomer, 1.4 g. of the pure 6-isomer, and an additional amount of unresolved product were recovered by chromatography.

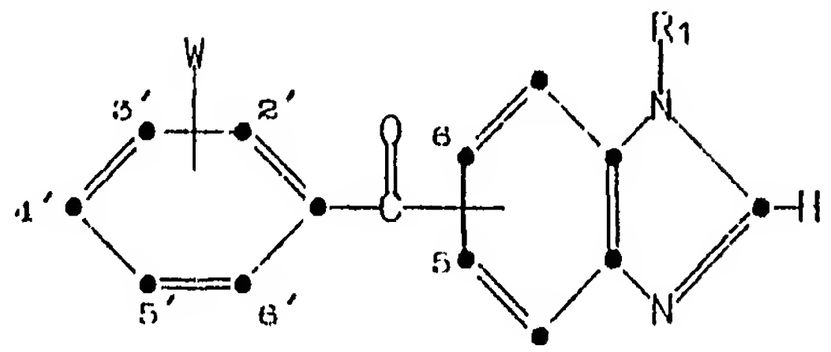
Examples 3-10

Following the procedure of Examples 1-2, the compounds of Table I were prepared using the appropriate benzimidazole and R_1X halide.

Some of the products were converted to the hydrochloride salt in the usual way. Those compounds which are the hydrochloride salt are marked with an asterisk (*).

In the following tables, "W" refers to the substitution in the phenyl ring. Some of the compounds were not resolved into the pure isomers and are referred to as "5/6". Compounds which were resolved into the pure isomers are designated "5" or "6".

Table I



Example No.	R_1	Isomer	W	M^+							Yield (g.)
3	benzyl	5/6	H	312	235	105	91	77			3.00
4	phenyl	6	H	298	221	193	105	77	51		2.12
5	p-nitro-phenyl	5/6	H	343	266	220	164	105	77		10.00
6	isopropyl	5/6	H	264	187	145	117	105	77		3.46
7*	isopropyl	6	H	264	187	145	117	105	77		--
8*	isopropyl	5	2',4',6'-trimethyl	306	277	235	187	147	119	117	2.60
9*	isopropyl	6	2',4',6'-trimethyl	306	289	277	187	147	119	117	1.60
10	morpholin-ylmethyl	5/6	H	321	222	145	100	77			20.13

Example 11

1-(2-pyridyl)-6-benzoylbenzimidazole

To a solution of 4.44 g. (20 mmoles) of 5(6)-benzoylbenzimidazole in 50 ml. of dimethylformamide was added 1.9 ml. (20 mmoles) of 2-chloropyridine. After adding 1 g. of sodium hydride (20 mmoles, 50% oil suspension), the reaction was heated to reflux overnight. The reaction was cooled and poured into ethyl acetate and the resulting suspension was washed three times with 300 ml. portions of a saturated sodium chloride solution. The organic solution was dried over magnesium sulfate and evaporated to dryness. The residue was chromatographed over silica gel eluting with 80% ethyl acetate/20% hexane, giving 1.01 g. of 1-(2-pyridyl)-5-benzoylbenzimidazole and 0.54 g. of 1-(2-pyridyl)-6-benzoylbenzimidazole.

1-(2-pyridyl)-5-benzoylbenzimidazole, M^+ = 299, 222, 194, 167, 105 and 77.

Analysis: $C_{13}H_{13}N_3O$;

Calc:. C, 76.24; H, 4.38; N, 14.04;

Found: C, 76.26; H, 4.66; N, 14.34.

1-(2-pyridyl)-6-benzoylbenzimidazole, M^+ = 299, 222, 194, 167, 105 and 77.

Analysis: $C_{13}H_{13}N_3O$;

Calc.: C, 76.24; H, 4.38; N, 14.04;

Found: C, 76.42; H, 4.28; N, 14.01.

Example 12

1-(Dimethylaminomethyl)-5(6)-benzoylbenzimidazole

A 40% aqueous solution of dimethylamine (11.3 ml., 100 mmoles) was added to a suspension of 22.3 g. (100 mmoles) of 5(6)-benzoylbenzimidazole in 300 ml. of methylene chloride, followed by the dropwise addition of 15 ml. of a 37% aqueous solution of formaldehyde. After stirring at room temperature for three days, the solution was extracted first with water, and then with 1N sodium hydroxide. The organic phase was dried over magnesium sulfate and was then evaporated. The resulting residue was crystallized from ethyl acetate to give 17.2 g. of the title products, M^+ = 279, 222, 145, 117, 105, and 77.

Analysis: $C_{17}H_{17}N_3O$;
Calc.: C, 73.10; H, 6.13; N, 15.04;
Found: C, 72.53; H, 6.11; N, 14.05.

General Preparation 1

The following typical procedures were used to regioselectively prepare 5- and 6-substituted-2-aminobenzimidazole compounds of Formula I.

A. Reaction of a 3-chloro-4-nitrobenzophenone with R_1NH_2.

1. Procedure when R_1NH_2 is a volatile amine

Fifty grams of the 3-chloro-4-nitrobenzophenone, 100 ml. of the amine, and 300 ml. of methanol were heated to about 145°C. for 16 hours in a stainless

steel autoclave. The reaction mixture was worked up by removing the solvent by evaporation, adding 6N hydrochloric acid, and heating to reflux for about 20 minutes. Upon cooling, ethyl acetate was added and 5N sodium hydroxide was added to a pH of about 9. The organic layer was separated, dried over magnesium sulfate, and evaporated. The product was purified by chromatography over silica gel eluting with 10% ethyl acetate/90% hexane. The 3-amino-4-nitrobenzophenone thus isolated was used without further purification for the subsequent step (B).

2. Procedure when R_1NH_2 is a non-volatile amine

About 15 g. of the chloronitrobenzophenone, 10 g. of anhydrous sodium carbonate, and one equivalent of the amine in 200 ml. of sulfolane were heated to 130-140°C. for 3 to 3.5 hours and worked up as described above.

3. Procedure when R_1NH_2 is an aromatic amine

The conditions utilized were the same as for non-volatile amines, except that the reaction mixture was heated to 180-190°C. for about 16 hours.

B. Hydrogenation of 3-amino-4-nitrobenzophenones to 3,4-diaminobenzophenones.

About 72 g. of the 3-amino-4-nitrobenzophenone were hydrogenated overnight in 2.9 L. of tetrahydrofuran under 4.22 kg/cm.^{2} at room temperature with about 15 g. of Raney nickel. The catalyst was removed

by filtration and the solvent was removed in vacuo. The resulting diaminobenzophenone was used without purification for the subsequent steps.

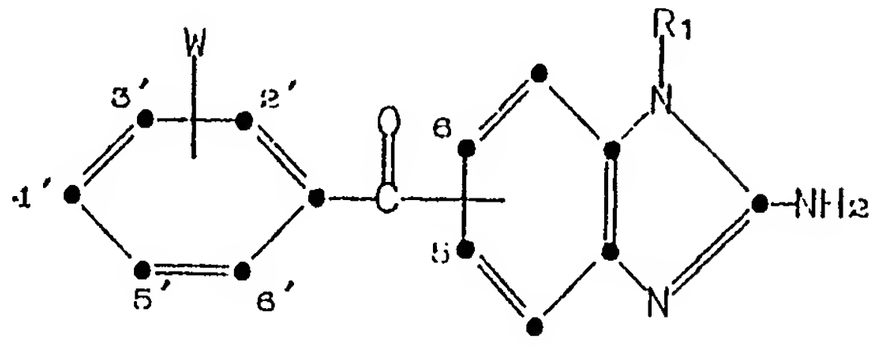
C. Preparation of 2-aminobenzimidazoles.

Equal molar amounts of the 3,4-diaminobenzophenone and cyanogen bromide were stirred overnight in 90% methanol/10% water. The methanol was then removed in vacuo and ethyl acetate was added. The solution was washed once with a saturated solution of sodium bicarbonate. The solution was then dried and evaporated to a solid residue. Column chromatography over silica gel eluting with a 0-5% step gradient of methanol in ethyl acetate gave the desired product in about a 60% yield.

Examples 13-19

Following the procedures of General Preparation 1, the compounds of Table II were prepared.

Table II



Example No.	R_1	Isomer	W	M^+									Yield (g.)
13	cyclohexyl	6	H	319	237	208	160	132	105	77	58	43	14.0
14	cyclohexyl	6	4'-OCH_3	349	334	267	160	135					1.5
15	cyclohexyl	6	4'-F	337	255	160	123						1.0
16	isopropyl	6	H	279	202	160	105	77					4.5
17*	isopropyl	6	H	279	202	160	132	105	77				--
18	phenyl	6	H	313	236	208	105	77					4.0
19	allyl	5	H	277	200	105	77						2.0

General Preparation 2

Using the substituted diaminobenzophenones of General Preparation 1 (A and B), the 2-unsubstituted benzimidazoles of Examples 1-11 could be prepared by the reaction with formic acid giving the pure 5- and 6-isomers.

In a typical preparation, 50 g. of the diamine were mixed with 50 ml. of 98% formic acid and 100 ml. of 6N hydrochloric acid. The mixture was refluxed for three hours, cooled, neutralized to a pH of about 7 with 2N sodium hydroxide, and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and evaporated to dryness. The residue was purified by column chromatography over silica gel, eluting with 70% ethyl acetate/30% hexane. The usual yield of the pure isomers was about 50%.

Example 20

1-isopropyl-2-(1-hydroxyethyl)-6-benzoyl-benzimidazole

Reacting 3-isopropylamino-4-aminobenzophenone, prepared by General Preparation 1 (A and B), with lactic acid according to the procedure of General Preparation 2 gave 2 g. the title product, M^+ = 308, 293, 265, 251, 231, 189, 171, 143, 117, 105, 77 and 43.

Analysis: $C_{19}H_{20}N_2O_2$;

Calc.: C, 74.00; H, 6.54; N, 9.08;

Found: C, 73.90; H, 6.40; N, 8.87.

Examples 21 and 22

1-(1-cyclohexenyl)-2-hydroxy-5-benzoylbenzimidazole and 1-(1-cyclohexenyl)-2-hydroxy-6-benzoylbenzimidazole

Ten grams of 3,4-diaminobenzophenone and eight milliliters of ethyl 2-cyclohexanone carboxylate were refluxed overnight in xylene. The resulting precipitate was filtered hot to give 2.7 g. of 1-(1-cyclohexenyl)-2-hydroxy-5-benzoylbenzimidazole, M^+ = 318, 241, 238, 213, 161, 133, 105 and 77.

The filtrate from above was cooled and concentrated in vacuo resulting in a precipitate which was recovered by filtration, affording 1.5 g. of pure 1-(1-cyclohexenyl)-2-hydroxy-6-benzoylbenzimidazole, M^+ = 318, 241, 238, 213, 161, 105, 91 and 77.

Analysis: $C_{20}H_{18}N_2O_2$;

Calc.: C, 75.45; H, 5.70; N, 8.80;

Found: C, 75.27; H, 5.68; N, 8.56.

Example 23

2-methylmercapto-1-benzyl-5(6)-benzoylbenzimidazole

A. Preparation of 2-thio-5(6)-benzoylbenzimidazole

Twenty grams (80.6 mmoles) of 3,4-diaminobenzophenone were dissolved in 300 ml. of methanol and 45 ml. of water. Potassium ethyl xanthate (12.9 g.,

80.6 mmoles) was added and the reaction mixture was heated to reflux for three hours. Twelve grams of decolorizing charcoal were added and the reaction was refluxed an additional ten minutes. The reaction mixture was cooled and filtered and the solvent of the filtrate was removed by evaporation. Ethyl acetate (200 ml.) was added. The organic solution was washed twice with a saturated solution of sodium chloride and once with 1N hydrochloric acid. The organic phase was dried over magnesium sulfate and evaporated to dryness. Crystallization of the residue from 30% ether/70% ethyl acetate gave 14.5 g. of 2-thio-5(6)-benzoylbenzimidazole.

B. Preparation of 2-methylmercapto-5(6)-benzoylbenzimidazole

Five grams of 2-thio-5(6)-benzoylbenzimidazole and five grams of sodium bicarbonate were added to 40 ml. of dimethylformamide, followed by 2.4 ml. of methyl iodide. After 15 minutes, the reaction mixture was added to 150 ml. of ethyl acetate.

The ethyl acetate solution was washed three times with a saturated solution of sodium chloride. The organic phase was dried over magnesium sulfate and evaporated. The resulting oil was washed with hexane to remove residual dimethylformamide, and the residue was crystallized from cold ether to give 1.7 g. of 2-methylmercapto-5(6)-benzoylbenzimidazole, $M^+ = 268$.

Analysis: $C_{15}H_{12}N_2OS$;
Calc.: C, 67.14; H, 4.51; N, 10.44;
S, 11.95;
Found: C, 67.12; H, 4.89; N, 10.14;
S, 11.97.

C. Preparation of 2-methylmercapto-1-benzyl-5(6)-benzoylbenzimidazole

2-Methylmercapto-5(6)-benzoylbenzimidazole (10 g.) was dissolved in 50 ml. of dimethylformamide, followed by 4.8 g. of sodium hydride and 4.43 ml. of bromotoluene. The reaction mixture was stirred at room temperature for four hours, then washed and poured into water. After 30 minutes, the reaction mixture was poured into ethyl acetate.

The ethyl acetate solution was washed three times with a saturated solution of sodium chloride. The organic phase was dried over magnesium sulfate and evaporated. To the residue was added ethyl ether and the mixture was chilled to about 0°C. The product crystallized and was purified by chromatography using 50% ethyl acetate/hexane to give 5 g. of 2-methylmercapto-1-benzyl-5(6)-benzoylbenzimidazole, M^+ = 358, 267, 105, 91 and 77.

General Preparation 3

The following general preparation was used to convert ketones (R_3 is $O=C(R_6)-$) to the corresponding oximes.

One gram of the ketone is dissolved in 15 ml. of methanol and 5 ml. of pyridine. One gram of hydroxylamine hydrochloride is added and the reaction is refluxed for three hours. The reaction is added to a mixture of 200 ml. of ethyl acetate and 200 ml. of a saturated solution of sodium chloride. The pH is adjusted to about 7 with 1N sodium hydroxide, and the organic layer is separated. The organic layer is dried over magnesium sulfate and evaporated. The desired oxime crystallizes on concentration of the solvent or the residue can be crystallized from small amounts of ethyl acetate. The reaction usually gives about a 50/50 mixture of the syn and anti isomers.

Examples 24-66

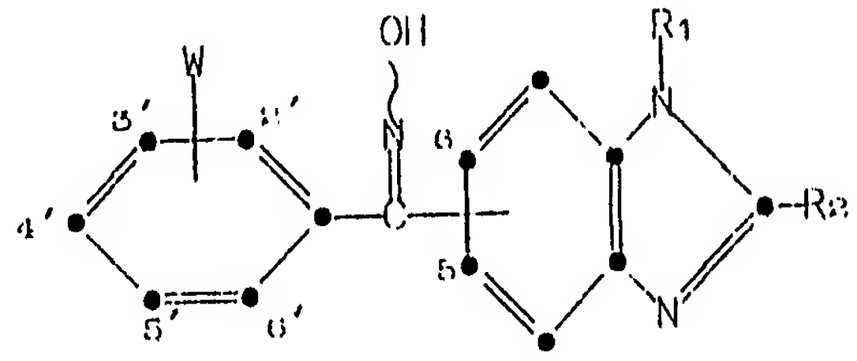
Following the procedure of General Preparation 3, the compounds of Examples 24-66 in Table III were prepared. Those examples marked with an asterisk (*) were converted to the hydrochloride salt from the free base in the following manner:

For oxime derivatives which were soluble in dilute hydrochloric acid, the oxime was dissolved in a minimum volume of 1N hydrochloric acid and the solution brought to dryness in vacuo. The residue was crystallized from a small volume of acetone to give the desired product.

For oxime derivatives that are not soluble in 1N hydrochloric acid, several equivalents of acetyl chloride was added to dry methanol, and the oxime was dissolved in the methanolic hydrogen chloride solution. Evaporation of the solvent gave the desired product which, if not already crystalline, could be crystallized from small volumes of acetone.

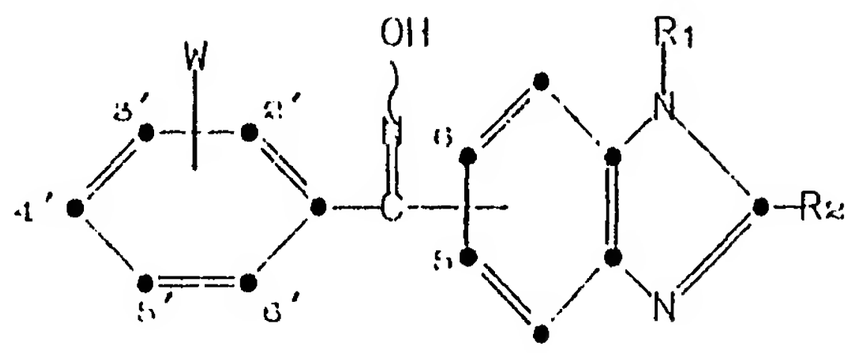
Some of the pure 5- and 6-isomers were prepared from the pure isomers of the corresponding ketone while others were resolved by crystallization and/or chromatography after a mixture of the oxime isomers was obtained by reacting hydroxylamine with a mixture of the 5- and 6-substituted ketones. All of the oxime derivatives were analyzed and tested as the mixture of syn and anti isomers.

Table III



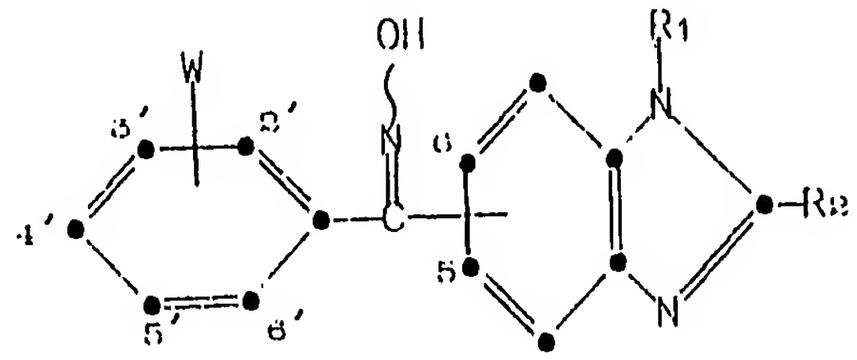
Example No.	R_1	R_2	Isomer	W	M^+	Yield (g.)
24	isopropyl	H	5/6	H	279 262 220 160 145 77	14.5
25*	isopropyl	H	6	H	279 264 262 220 160 145 77	--
26	isopropyl	H	5	H	279 262 220 160 145 90 77	0.4
27*	isopropyl	H	5	H	279 262 220 187 145 117 105 77	--
28	cyclohexyl	H	5/6	H	319 302 220 145 105 77	0.09
29*	cyclohexyl	H	6	H	319 302 220 200 145 118 105 77	--
30	benzyl	H	6	H	327 310 219 208 91 77	0.96
31	benzyl	H	5	H	327 310 219 208 105 91 77	0.49
32	phenyl	H	6	H	313 296 194 166 91 77 51	0.60
33*	phenyl	H	6	H	313 296 194 166 77	0.30
34	phenyl	H	6	4'-chloro	347 330 296 194 166 139 77	0.33

Table III cont'd.



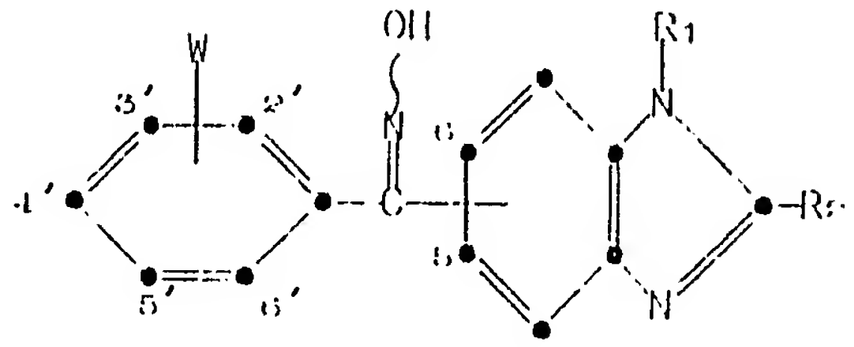
Example No.	R_1	R_2	Isomer	W	M^+									Yield (g.)
35	p-nitro-phenyl	H	5/6	H	358	341	295	239	115	77				1.4
36**	p-amino-phenyl	H	5/6	H	328	311	251	209	179	77	65			0.6
37	2-pyridyl	H	6	H	314	297	195	164	106	78	77			0.11
38	2-pyridyl	H	5	H	314	297	195	167	105	78	77			0.11
39	1-adamantyl	H	6	H	371	355	135	107	93	79				0.9
40	cyclopropyl	H	6	H	277	260	157	131	77	41				0.9
41	n-hexyl	H	6	H	321	304	220	202	131	77				1.5
42	n-hexyl	H	5	H	321	304	220	202	131	105	77			0.71
43	allyl	H	5	H	277	260	219	205	156	103	77	41		0.6
44	allyl	H	6	H	277	260	219	205	156	103	77	41		1.1
45	2-thiazolyl	H	6	H	320	303	217	201	105	77				0.3
46	morpholin-ylmethyl	H	5/6	H	336	237	220	100	77					2.2
47	$CH_2CH(OH)CH_3$	H	6	H	295	278	250	234	176	130	103	77	45	1.5

Table III cont'd.



Example No.	R_1	R_2	Isomer	W	M^+										Yield (g.)
48	t-butyl	H	6	H	293	277	237	220	195	118	93	79			0.5
49	cyclohexyl	NH_2	6	H	334	318	252	235	215	133	105	79	61		1.0
50	cyclohexyl	NH_2	6	4'-OCH_3	364	348	265	215	133	105	77	55			0.75
51	cyclohexyl	NH_2	6	3'-CH_3	348	331	249	215	133	105	79				0.5
52	cyclohexyl	NH_2	6	2'-CH_3	348	331	249	133	105	91					1.0
53	cyclohexyl	NH_2	6	4'-F	352	336	253	133	105	55	41				0.7
54	2-pyridyl	NH_2	6	H	(D)	252	235	133	105	77					0.26
55	1-adamantyl	NH_2	6	H	386	370	234	135	93	79					0.22
56*	isopropyl	NH_2	6	H	294	277	264	235	133	105	77				--
57	$CH_2CH(OH)CH_3$	NH_2	6	H	310	293	249	191	145	77	45				0.75
58	isopropyl	NH_2	6	H	294	277	264	235	175	133	91	77	51	43	3.0
59	phenyl	NH_2	6	H	328	311	233	209	167	165	77	63	51		0.4
60	2-pyridyl	NH_2	5	H	329	313	252	235	220	133	105	77			0.08
61	allyl	NH_2	5	H	292	275	234	220	173	132	104	77			0.36
62	1-cyclohexenyl	OH	5	H	333	317	316	288	253	236	214	134	104	79	52	0.53

Table III cont'd.



Example No.	R_1	R_2	Isomer	W	M^+	Yield (g.)
63	1-cyclohexenyl	OH	6	H	333 317 288 253 236 214 134 104 79	0.95
64	isopropyl	$CH(OH)-CH_3$	6	H	323 306 266 144 118 77	0.80
65	benzyl	SCH_3	5	H	373 356 282 162 91 77	0.46
66	benzyl	SCH_3	6	H	373 356 282 162 91 77	0.62

* - hydrochloride salt

** - prepared from the p-nitrophenyl derivative, Ex. 35, by reduction.

D - m/e = 252 (M^+ -77)

Example 67

1-(dimethylaminomethyl)-5(6)-(α-hydroxyiminobenzyl)benzimidazole

To a suspension of 7.11 g. (30 mmoles) of 5(6)-(α-hydroxyiminobenzyl)benzimidazole, in 90 ml. of methylene chloride was added 3.4 ml. of a 40% aqueous solution of dimethylamine, followed by 4.5 ml. of a 37% aqueous solution of formaldehyde. The reaction was stirred for three days at room temperature and then washed with 100 ml. of 1N sodium hydroxide. The organic layer was separated, dried over magnesium sulfate, and removed by evaporation to give a gum. Crystallization of the gum from 20 ml. of 50% aqueous methanol gave 1.95 g. of a mixture of the title isomers, M^+ = 237 (M^+-57), 220, 205, 134, 118, 105, 90 and 77.

Example 68

1-isopropyl-2-isopropylamino-5(6)-(α-hydroxyiminobenzyl)benzimidazole

When 2-amino-5(6)-benzoylbenzimidazole was treated with two equivalents of sodium hydride and an excess of isopropyl bromide according to the procedure of Examples 1-2, the dialkylated 1-isopropyl-2-isopropylamino-5(6)-benzoylbenzimidazole products were obtained. Treatment of this intermediate with hydroxylamine hydrochloride according to the procedure of Preparation 3 gave the title products, yield 240 mg., as an isomeric mixture, M^+ = 336, 252, 235, 220, 159, 133, 105 and 77.

Analysis: $C_{20}H_{24}N_4O$;

Calc.: C, 71.40; H, 7.19; N, 16.65;

Found: C, 71.63; H, 7.24; N, 16.47.

Example 69

1-isopropyl-2-amino-6-(1-phenylethenyl)-benzimidazole

Three grams (10.7 mmoles) of 1-isopropyl-2-amino-6-benzoylbenzimidazole were dissolved in 25 ml. of tetrahydrofuran, after which was added 27 ml. of a 2M solution of methyl magnesium bromide in ethyl ether. After stirring overnight, ethyl acetate was added, and the solution was washed three times with a saturated sodium chloride solution. The organic solution was dried over magnesium sulfate, filtered, and evaporated under reduced pressure. One hundred milliliters of 98% formic acid were added to the residue. The solution was refluxed for 2 hours. The formic acid was evaporated under reduced pressure. Ethyl acetate was added, and the resulting solution was washed with a saturated sodium bicarbonate solution. After drying over magnesium sulfate, the solution was filtered and concentrated. Upon the addition of a small volume of ether, 2.0 g. of the title product solidified out of solution which was recovered by filtration, M^+ = 277, 235, 193, 165 and 77.

Example 70

1-isopropyl-2-amino-6-(1-phenyl-1-propenyl)-benzimidazole

Following the procedure of Example 69, 1-isopropyl-2-amino-6-benzoylbenzimidazole and ethyl magnesium bromide were reacted to give the title product, yield 600 mg., as both the cis and trans alkylene isomers, M^+ = 291, 279, 264, 248, 220, 202, 160 and 43.

Example 71

1-isopropyl-2-amino-6-(1-phenyl-2-bromoethenyl)benzimidazole

Three hundred milligrams (1.08 mmoles) of 1-isopropyl-2-amino-6-(1-phenylethenyl)benzimidazole and 192 mg. (1.08 mmoles) of N-bromosuccinimide were refluxed overnight in 20 ml. of dry tetrahydrofuran. After cooling, ethyl acetate was added and the solution was washed with a saturated solution of sodium bicarbonate. The organic layer was dried over magnesium sulfate, filtered, and evaporated in vacuo. The residue was chromatographed over silica gel, first eluting with ethyl acetate to remove impurities, and then with 10% methanol/90% ethyl acetate. The title product was crystallized from ether giving 200 mg. of the cis/trans mixture, M^+ = 357, 313, 276, 234, 190, 165, 102, 77 and 43.

Analysis: $C_{18}H_{18}BrN_3$;

Calc.: C, 60.68; H, 5.09; N, 11.79; Br, 22.43;

Found: C, 60.58; H, 5.24; N, 11.95; Br, 22.13.

Example 72

1-isopropyl-2-amino-6-(1-phenyl-2-cyano-ethenyl)benzimidazole

Forty millimoles (2.1 ml.) of dry acetonitrile were added to 30 ml. of tetrahydrofuran. A nitrogen blanket was applied and the temperature of the solution lowered to about -78°C. by means of an external acetone/dry ice bath. Twenty-five milliliters of a 1.6M solution of n-butyl lithium were added. After stirring at -78°C. for 30 minutes, a solution of 2.8 g. (10 mmoles) of 1-isopropyl-2-amino-6-benzoylbenzimidazole in 30 ml. of tetrahydrofuran was added. The reaction solution was allowed to warm to about -20°C. and was then stirred for 5 hours at -20 to -5°C. Water and ethyl acetate were then added and the layers were separated. The organic layer was dried over magnesium sulfate, filtered, and evaporated in vacuo. The residue was dissolved in 100 ml. of 98% formic acid. After stirring on a hot water bath for 2.5 hours, the solution was evaporated under reduced pressure. The residue was dissolved in ethyl acetate and washed with a saturated solution of sodium bicarbonate. The organic solution was dried over magnesium sulfate, filtered, and evaporated. The residue was chromatographed over silica gel, eluting first with ethyl acetate to remove

non-polar impurities, then with 10% methanol/90% ethyl acetate to elute the title product. The product was further purified by reverse phase chromatography, eluting with 60% aqueous methanol, followed by crystallization from methyl ethyl ketone, resulting in 350 mg. of the title product, M^+ = 302, 270, 260, 236, 202, 160, 132, 105, 77 and 43.

Example 73

1-phenyl-2-amino-6-(1-phenyl-2-cyanoethenyl)-benzimidazole

Following the procedure of Example 72, 3.1 g. of 1-phenyl-2-amino-6-benzoylbenzimidazole was transformed into 300 mg. of the title product, M^+ = 336, 259, 190, 168 and 77.

Analysis: $C_{22}H_{16}N_4$;

Calc.: C, 78.55; H, 4.79; N, 16.66;

Found: C, 78.51; H, 4.52; N, 16.85.

Example 74

anti-3-(1-isopropyl-2-aminobenzimidazol-6-yl)-3-phenyl-2-propenamide hydrochloride

A solution of 8.37 g. of 1-isopropyl-2-amino-6-benzoylbenzimidazole in tetrahydrofuran was added to a solution of 95 ml. of a 1.6M solution of n-butyl lithium and 30.45 g. of bis(trimethylsilyl)acetamide in tetrahydrofuran which was previously cooled to about -70°C. The reaction was stirred for about two hours and the temperature was allowed to warm to about -10°C.

The reaction was poured into an ice/ammonium chloride solution. The organic layer was separated, washed with water, and dried, giving both the syn- and anti-isomers of the title compound. Yield 50 mg. The residue was dissolved in a small volume of methyl ethyl ketone. After standing at room temperature overnight, the resulting crystals were recovered by filtration and identified as syn-3-(1-isopropyl-2-aminobenzimidazol-6-yl)-3-phenyl-2-propenamide, M^+ = 320, 303, 277, 234, 190 and 105.

Analysis: $C_{19}H_{20}N_4O$;

Calc.: C, 71.24; H, 6.47; N, 17.27; O, 5.19;

Found: C, 71.23; N, 6.29; N, 17.49; O, 4.99.

The mother liquor from the above product was evaporated, and the residue was dissolved in pyridine. Excess thionyl chloride was added and the solution was stirred at room temperature overnight. The reaction mixture was evaporated to dryness in vacuo. Water and ethyl acetate were added to the residue. The layers were separated and the water layer was adjusted to a pH of about 8. The water layer was extracted with ethyl acetate. The ethyl acetate was dried and evaporated to dryness to give the title anti-3-(1-isopropyl-2-aminobenzimidazol-6-yl)-3-phenyl-2-propenamide hydrochloride.

Analysis: $C_{19}H_{20}N_4O \cdot HCl$;

Calc.: C, 63.19; H, 6.03; N, 15.04; O, 6.30; Cl, 9.74;

Found: C, 63.95; H, 5.93; N, 15.70; O, 4.48; Cl, 9.93.

The following formulation examples may employ as active ingredients any of the pharmaceutical compounds of formula I.

Example 75

Preparation of Tablets

	Per Tablet
1-cyclohexyl-2-amino-6-(α-hydroxyiminobenzyl)benzimidazole	250 mg.
Lactose	200 mg.
Corn starch	300 mg.
Corn starch paste	50 mg.
Calcium stearate	5 mg.
Dicalcium phosphate	45 mg.

The benzimidazole, corn starch, lactose and dicalcium phosphate are uniformly blended. The corn starch paste is prepared as a 10 percent aqueous paste and is blended into the mixture to uniformity. The mixture is blended with the calcium stearate and then compressed in tablets each weighing 850 mg.

Example 76

Preparation for Suppositories

	Per suppository
1-isopropyl-5-acetylbenzimidazole	500 mg.
Theobroma oil	1500 mg.

The above ingredients are blended to uniformity at a temperature of about 60°C., poured into a suppository mold of nominal 2 g. capacity, and allowed to cool.

Example 77

Preparation for Oral Suspension

	Per 100 ml.
1-Ethyl-2-acetamido-6-(1-phenyl-2-bromoethenyl)benzimidazole	500 mg.
Sorbitol solution (70% N.F.)	40 ml.
Sodium benzoate	150 mg.
Lactose	10 mg.
Cherry flavor	50 mg.
Water	q.s. to 100 ml.

The above ingredients are combined such that each ml. of syrup contains 5 mg. of active ingredient.

Example 78

Intranasal Formulation

	Percent by weight
1-(4-methoxyphenyl)-2-methyl-mercapto-6-[(α-ethenyl)-cyclo-hexylmethyl]benzimidazole	1.0
Antarox (non-ionic polyoxyethylated fixed oil, GAF Corp.)	38.5
Ethanol	10.0
Freon 11 (trichloromonofluoro-methane)	25.0
Freon 12 (dichlorodifluoromethane)	25.0
Menthol	0.5

The benzimidazole is added to the Antarox at about 70-80°C. and the mixture is stirred until a solution is formed. The solution is cooled and diluted with a mixture of the menthol in the ethanol. The

resulting solution is placed in an aerosol container and chilled to 0°C., the Freon propellants are added, and the aerosol container is sealed with a valve.

The compounds of formula I were tested by the following method.

African green monkey kidney cells (BSC-1) or Hela cells (5-3) were grown in 25 cc. Falcon flasks at 37°C. in medium 199 with 5 percent inactivated fetal bovine serum (FBS), penicillin (150 units per ml.) and streptomycin (150 mcg./ml.). When confluent monolayers were formed, the supernatant growth medium was removed and 0.3 ml. of an appropriate dilution of virus (echo, Mengo, Coxsackie, polio or rhinovirus) was added to each flask. After absorption for one hour at room temperature, the virus infected cell sheet was overlaid with a medium comprising one part of 1 percent Ionagar No. 2 and one part double strength medium 199 with FBS, penicillin, and streptomycin which contains test compound at concentrations of about 100, 50, 25, 12, 6, 3, 1.5, 0.75, and 0, and/or 12.5, 6.25, 3.12, 1.56, 0.78, 0.39, 0.19, 0.09, 0.04, and 0.02 micrograms per milliliter (mcg./ml.). The flask containing no test compound served as the control for the test. The stock solutions of benzimidazole compounds were made up in dimethylsulfoxide solution at a concentration of 10^4 mcg./ml. The flasks were incubated for 72 hours at 37°C. for polio, Coxsackie, echo, and Mengo virus and 120 hours at 32°C. for rhinovirus. Plaques were seen in those areas where the virus infected and reproduced in the cells. A solution of 10 percent formalin and 2 percent sodium acetate was added to each flask to

inactivate the virus and fix the cell sheet to the surface of the flask. The virus plaques, irrespective of size, were counted after staining the surrounding cell areas with crystal violet. The plaque count was compared to the control count at each test concentration. The activity of the test compound was expressed as percentage plaque reduction, or percent inhibition. Alternatively, the test concentration which inhibits plaque formation by 50 percent can be used as a measure of activity. The 50 percent inhibition is indicated by the symbol I_{50}.

Test results are expressed in terms of Polio virus type I inhibition because the virus is easy to grow and consistent test results are obtained. However, the activity of the preferred compounds was confirmed against other virus cultures such as Coxsackie (A9, A21, B5), echovirus (strains 1-4), Mengo, rhinovirus (25 strains) and Polio (type I, II, III). Test results for various benzimidazole compounds are summarized in Table IV below where column 1 gives the Example number from the previous chemical examples, column 2 gives the 5(6)-position of the corresponding benzimidazole product, and column 3 indicates the test compound concentration in micrograms per milliliter (mcg./ml.) which inhibits Polio I plaque formation by 50 percent (I_{50}). In each case, 1-isopropylsulfonyl-2-amino-6-(syn-α-hydroxyiminobenzyl)benzimidazole was tested as a standard reference and gave an I_{50} in the range of 0.2-0.8 mcg./ml.

Table IV

Polio I Plaque Reduction of 1-Substituted-5(6)-Substituted-Benzimidazoles

Example No.	Isomer	I_{50} (mcg./ml.)**
2	6	0.78
6	5/6	6.0
8	5	6.25
9	6	6.25
10	5/6	25
11	6	12.5
12	5/6	12.5
18	6	0.78
21	5	>100
22	6	6
24	5/6	0.19
25*	6	0.39
26	5	25
27*	5	25
28	5/6	0.19
29*	6	0.78
30	6	0.39
31	5	25
32	6	0.09
33*	6	0.09
34	6	0.19
35	5/6	0.75
36	5/6	0.09
37	6	0.75
38	5	>100
39	6	25
40	6	0.39

Table IV cont'd.

Polio I Plaque Reduction of 1-Substituted-5(6)-Substituted-Benzimidazoles

Example No.	Isomer	I_{50} (mcg./ml.)**
41	6	0.78
42	5	100
44	6	0.78
45	6	0.78
46	5/6	6
47	6	6.25
48	6	0.19
49	6	0.09
50	6	0.09
51	6	3.12
52	6	0.78
53	6	1.5
54	6	6
55	6	0.75
57	6	3.12
58	6	0.09
59	6	0.09
60	5	6
62	5	3
63	6	3
64	6	1.5
65	5	50
66	6	25
67	5/6	6
68	5/6	3
69	6	1.56

Table IV cont'd.

Polio I Plaque Reduction of 1-Substituted-5(6)-Substituted-Benzimidazoles

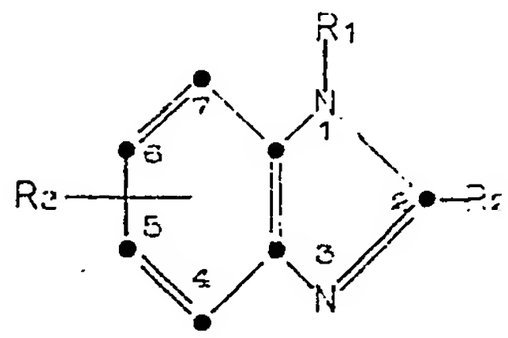
Example No.	Isomer	I_{50} (mcg./ml.)**
70	6	0.78
71	6	0.09
72	6	0.04
74*	6	0.39

*-hydrochloride salt

**-Drug concentration in micrograms per milliliter

CLAIMS

1. A benzimidazole compound of the formula



(I)

wherein:

R_1 is C_1-C_8 alkyl, C_2-C_8 alkenyl, C_3-C_7 cycloalkyl, C_5-C_7 cycloalken-1-yl, 2-pyridyl, 2-thiazolyl, adamantyl, hydroxy-substituted C_1-C_8 alkyl, unsubstituted or substituted phenyl, unsubstituted or substituted benzyl, or $R_4R_5NCH_2$- , where R_4 and R_5 are independently C_1-C_3 alkyl or R_4 and R_5, when taken together with the nitrogen atom to which they are attached, are pyrrolidino, piperidino, or morpholino;

R_2 is hydrogen, amino, C_1-C_4 alkylamino, methylmercapto, hydroxy, C_1-C_4 acylamino, or 1-hydroxyethyl;

R_3 is C_2-C_8 alkanoyloxy, unsubstituted or substituted phenylacetoxy, unsubstituted or substituted benzoyloxy, or $R_6\overset{\overset{Z}{\|}}{C}$- ;

Z is oxygen, hydroxyimino, C_1-C_4 alkoxyimino, C_1-C_4 acyloxyimino, hydrazono, C_1-C_7 alkylidene, =CHBr, =CHCl, =CBr_2, =CCl_2, =CBrCl, =CHCN, =$CHCONH_2$, or =$CHCO_2$(C_1-C_4 alkyl);

R_6 is C_1-C_7 alkyl, C_3-C_7 cycloalkyl, (C_3-C_7 cycloalkyl)methyl, 2-(C_3-C_7 cycloalkyl)ethyl, unsubstituted or substituted benzyl, unsubstituted or substituted phenyl; and

R_3 is at the 5 or 6 position,

subject to the limitation that when R_2 is hydroxy, R_1 may only be C_5-C_7 cycloalken-1-yl; and the pharmaceutically acceptable salts thereof.

2. A compound of formula I of claim 1, wherein:

R_1 is C_1-C_8 alkyl, C_2-C_8 alkenyl, phenyl, substituted phenyl, or C_3-C_7 cycloalkyl;

R_2 is hydrogen or amino; and

R_3 is $R_6C(=Z)$- wherein R_6 is phenyl or substituted phenyl.

3. A compound of formula I of claim 1, wherein:

R_1 is isopropyl, cyclohexyl or phenyl;

R_2 is hydrogen or amino; and

R_3 is $R_6C(=Z)$- wherein R_6 is phenyl and Z is oxygen, hydroxyimino, =CHBr, =CHCN, $=CHCH_3$, or $=CHCONH_2$.

4. A compound of formula I of claim 1, 2 or 3, wherein R_3 is at the 6 position.

5. Any one of the following compounds or its pharmaceutically acceptable salt:

1-isopropyl-2-amino-6-(1-phenyl-1-propenyl)-benzimidazole,

1-isopropyl-2-amino-6-(1-phenyl-2-cyanoethenyl)-benzimidazole,

1-phenyl-2-amino-6-(1-phenyl-2-cyanoethenyl)-benzimidazole,

1-isopropyl-2-amino-6-(1-phenyl-2-bromoethenyl)-benzimidazole,

3-(1-isopropyl-2-amino-benzimidazol-6-yl)-3-phenyl-2-propenamide,

1-isopropyl-2-amino-6-(α-hydroxyiminobenzyl)-benzimidazole,

1-phenyl-2-amino-6-(α-hydroxyiminobenzyl)-benzimidazole,

1-cyclohexyl-2-amino-6-(α-hydroxyiminobenzyl)-benzimidazole,

1-cyclohexyl-2-amino-6-(α-hydroxyimino-4'-methoxybenzyl)benzimidazole,

1-(t-butyl)-6-(α-hydroxyiminobenzyl)benzimidazole.

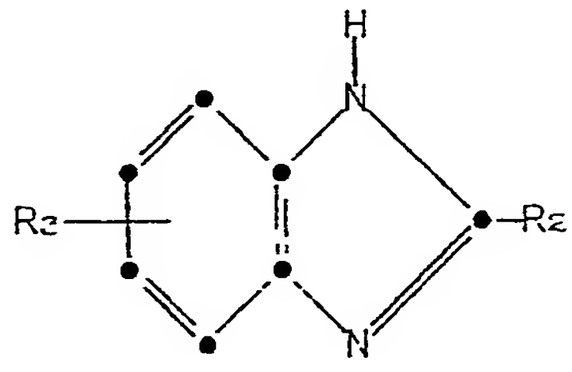
6. A benzimidazole derivative of formula I, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 5 for use as an antiviral agent.

7. A pharmaceutical formulation comprising as active ingredient a benzimidazole derivative of formula I, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 5 with one or more pharmaceutically acceptable carriers.

8. A pharmaceutical formulation of claim 7 wherein the active ingredient is formulated as a tablet, capsule or nasal formulation.

9. A process for preparing the compounds of formula I as defined in claim 1, which process comprises:

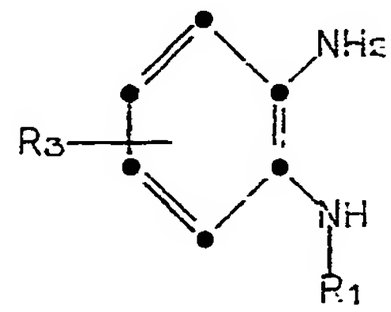
(A) alkylating a benzimidazole compound of the formula



(II)

wherein R_3 is defined as above and R_2 is other than hydroxy or amino, with a compound of the formula R_1X where R_1 is defined as above and X is fluoro, chloro, bromo, or iodo, to provide the compounds of formula I where R_2 is other than hydroxy or amino; or

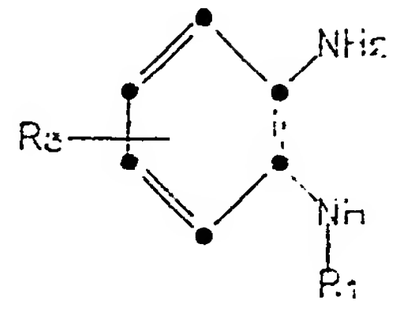
(B) heating a compound of the formula



(V)

wherein R_1 and R_3 are defined as above, with formic acid or lactic acid, preferably in the presence of a mineral acid, to provide the compounds of formula I wherein R_2 is hydrogen or 1-hydroxyethyl; or

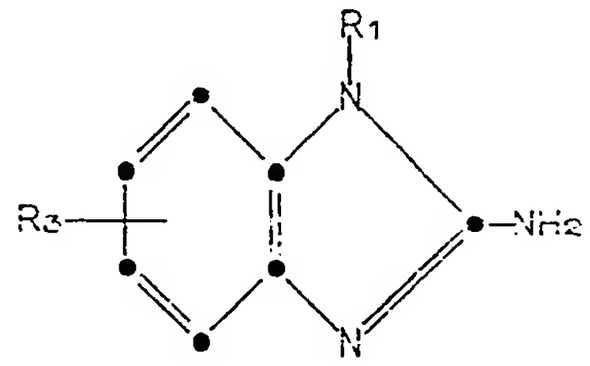
(C) cyclizing a compound of the formula



(V)

wherein R_1 and R_3 are defined as above, with cyanogen halide, to provide the compounds of formula I wherein R_2 is amino; or

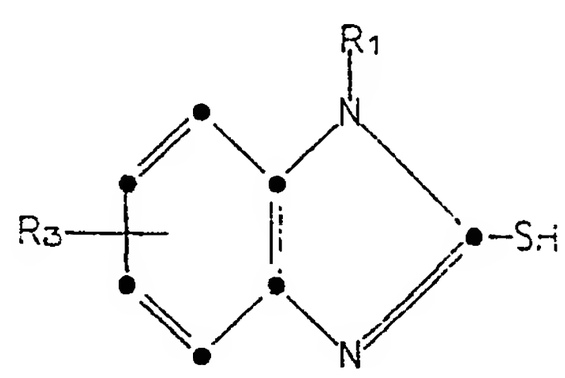
(D) alkylating a benzimidazole compound of the formula



(IB)

wherein R_1 and R_3 are defined as above, with a C_1-C_4 alkyl halide, to provide the compounds of formula I wherein R_2 is C_1-C_4 alkylamino; or

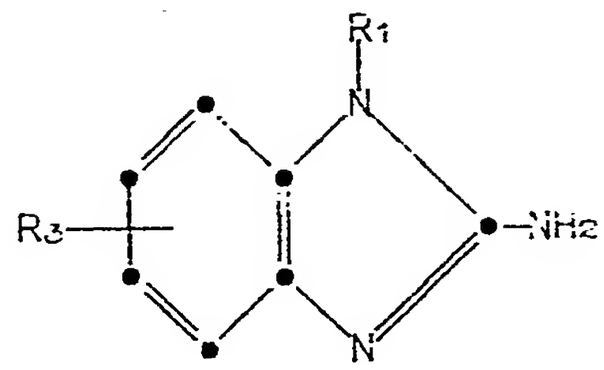
(E) alkylating a benzimidazole compound of the formula



(IC)

wherein R_1 and R_3 are defined as above, with methyl halide in the presence of a weak base, to provide the compounds of formula I wherein R_2 is methylmercapto; or

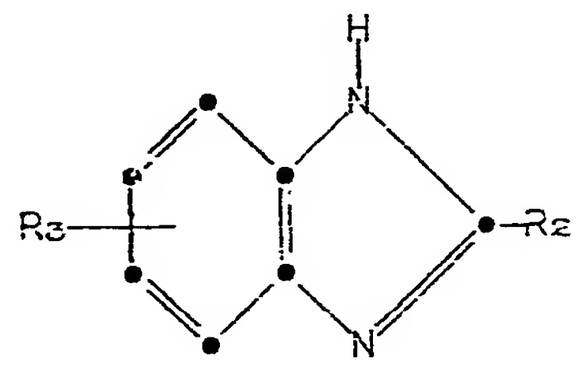
(F) acylating a benzimidazole compound of the formula



(IB)

wherein R_1 and R_3 are defined as above, with a C_2-C_4 anhydride, a mixed anhydride of formic and acetic anhydride, or a C_1-C_4 acyl halide, to provide the compounds of formula I wherein R_2 is C_1-C_4 acylamino; or

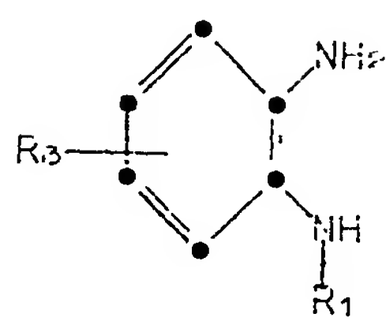
(G) reacting a benzimidazole compound of the formula



(II)

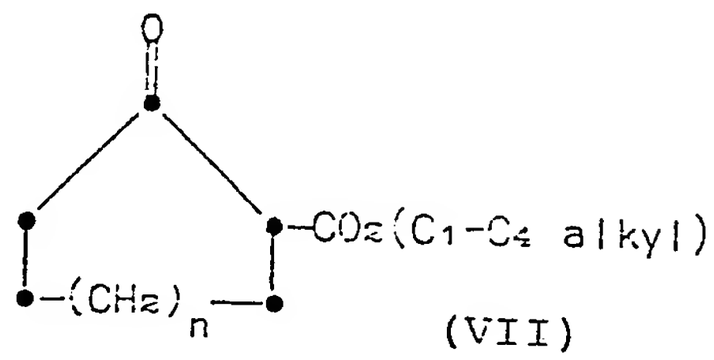
wherein R_2 and R_3 are defined as above, with R_4R_5NH, where R_4 and R_5 are defined as above, and formaldehyde, to provide the compounds of formula I wherein R_1 is $R_4R_5NCH_2$-; or

(H) condensing a compound of the formula



(V)

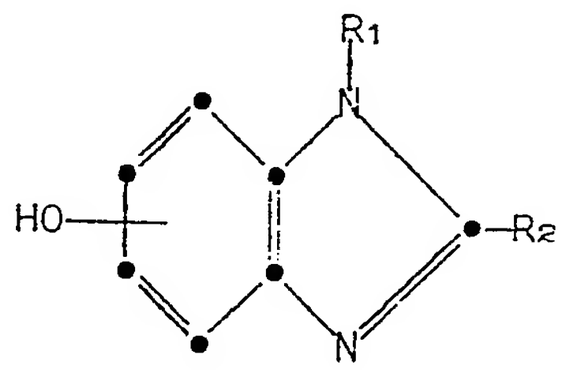
wherein R_1 and R_3 are defined as above, with a β-keto ester of the formula



(VII)

wherein n is 0-2, to provide the compounds of formula I wherein R_2 is hydrogen and R_1 is C_5-C_7 cycloalken-1-yl; or

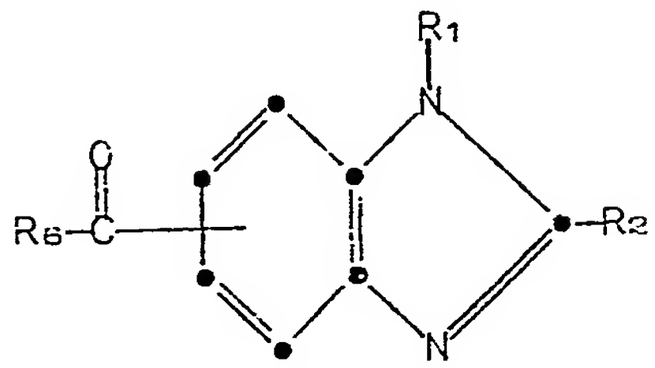
(I) esterifying a benzimidazole compound of the formula



(ID)

wherein R_1 is defined as above, and R_2 does not contain a hydroxy group, with an anhydride or acyl halide, to provide the compounds of formula I wherein R_3 is C_2-C_8 alkanoyloxy, unsubstituted or substituted phenylacetoxy, or unsubstituted or substituted benzoyloxy; or

(J) reacting a benzimidazole compound of the formula



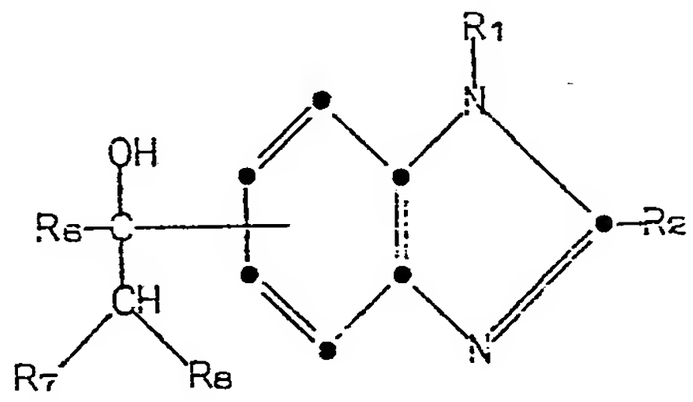
(IA)

wherein R_1, R_2 and R_6 are defined as above, with hydroxylamine, or its hydrochloride salt, hydrazine or C_1-C_4 alkoxyamine, to provide the compounds of formula I wherein Z is hydroxyimino, hydrazono, or C_1-C_4 alkoxyimino; or

(K) acylating a compound of formula I wherein Z is hydroxyimino with a C_1-C_4 anhydride or a C_1-C_4 acyl halide, to provide the compounds of formula I wherein Z is C_1-C_4 acyloxyimino; or

(L) etherifying a compound of formula I wherein Z is hydroxyimino with a C_1-C_4 alkyl halide, or alkylating the compound of formula I where R_3 is R_6-$\overset{\overset{O}{\|}}{C}$- with a C_1-C_4 alkoxyamine, to provide the compounds of formula I wherein Z is C_1-C_4 alkoxyimino; or

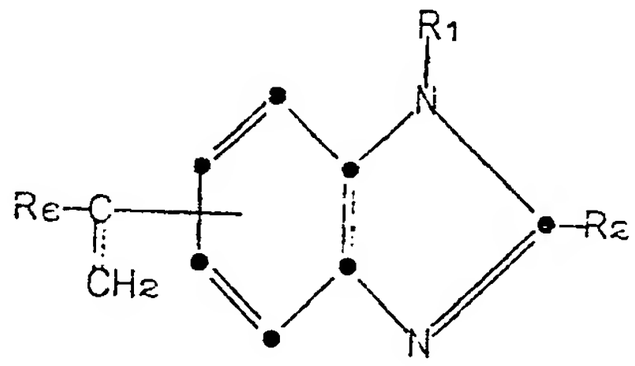
(M) dehydrating a benzimidazole compound of the formula



(IF)

wherein R_1, R_2 and R_6 are defined as above, and one of R_7 and R_8 is hydrogen and the other of R_7 and R_8 is hydrogen, C_1-C_6 alkyl, -CN, $-CONH_2$, or $-CO_2-(C_1-C_4$ alkyl), with an acid, to provide the compounds of formula I wherein Z is C_1-C_7 alkylidene, =CHCN, $=CHCONH_2$, or $=CHCO_2(C_1-C_4$ alkyl); or

(N) reacting a benzimidazole compound of the formula



(IGc)

wherein R_1, R_2 and R_6 are defined as above, with a halogenating agent, to provide the compounds of formula I wherein Z is =CHBr, =CHCl, $=CBr_2$, $=CCl_2$, or =CBrCl; or

(O) resolving the benzimidazole compounds of formula I into its 5 and 6 isomers; or

(P) resolving the benzimidazole compounds of formula I wherein Z is hydroxyimino, C_1-C_4 alkoxyimino, C_1-C_4 acyloxyimino, or hydrazono into its <u>syn</u> and <u>anti</u> isomers; or

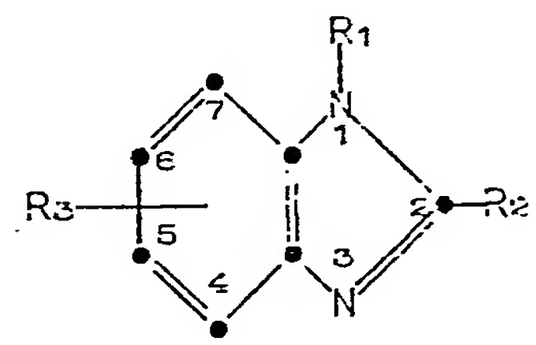
(Q) resolving the benzimidazole compounds of formula I wherein Z is C_1-C_7 alkylidene, =CHBr, =CHCl, $=CBr_2$, $=CCl_2$, =CBrCl, =CHCN, $=CHCONH_2$ or $=CHCO_2(C_1-C_4$ alkyl) into its <u>cis</u> and <u>trans</u> isomers; or

(R) salifying the compounds of formula I to form pharmaceutically acceptable salts.

X-5513-(P)

CLAIMS

1. A process for preparing a benzimidazole compound of the formula



(I)

wherein:

R_1 is C_1-C_8 alkyl, C_2-C_8 alkenyl, C_3-C_7 cycloalkyl, C_5-C_7 cycloalken-1-yl, 2-pyridyl, 2-thiazolyl, adamantyl, hydroxy-substituted C_1-C_8 alkyl, unsubstituted or substituted phenyl, unsubstituted or substituted benzyl, or $R_4R_5NCH_2$- , where R_4 and R_5 are independently C_1-C_3 alkyl or R_4 and R_5, when taken together with the nitrogen atom to which they are attached, are pyrrolidino, piperidino, or morpholino;

R_2 is hydrogen, amino, C_1-C_4 alkylamino, methylmercapto, hydroxy, C_1-C_4 acylamino, or 1-hydroxyethyl;

R_3 is C_2-C_8 alkanoyloxy, unsubstituted or substituted phenylacetoxy, unsubstituted or substituted benzoyloxy, or $R_6\overset{\overset{Z}{\|}}{C}-$;

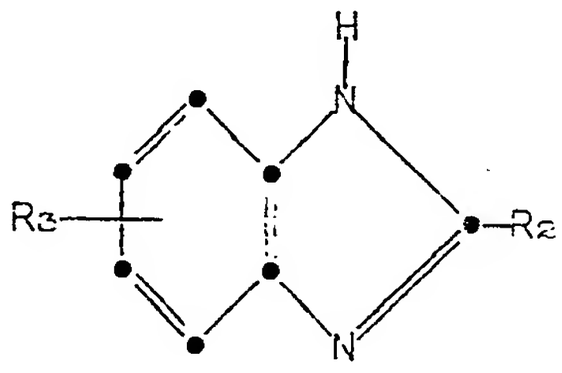
Z is oxygen, hydroxyimino, C_1-C_4 alkoxyimino, C_1-C_4 acyloxyimino, hydrazono, C_1-C_7 alkylidene, =CHBr, =CHCl, $=CBr_2$, $=CCl_2$, =CBrCl, =CHCN, $=CHCONH_2$, or $=CHCO_2$(C_1-C_4 alkyl);

R_6 is C_1-C_7 alkyl, C_3-C_7 cycloalkyl, (C_3-C_7 cycloalkyl)methyl, 2-(C_3-C_7 cycloalkyl)ethyl, unsubstituted or substituted benzyl, unsubstituted or substituted phenyl; and

R_3 is at the 5 or 6 position,

subject to the limitation that when R_2 is hydroxy, R_1 may only be C_5-C_7 cycloalken-1-yl; and the pharmaceutically acceptable salts thereof, which process comprises:

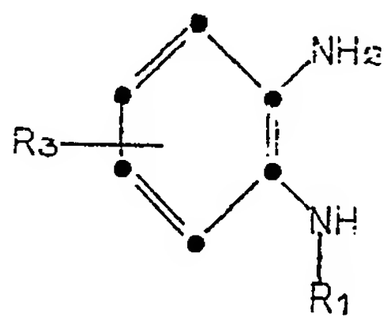
(A) alkylating a benzimidazole compound of the formula



(II)

wherein R_3 is defined as above and R_2 is other than hydroxy or amino, with a compound of the formula R_1X where R_1 is defined as above and X is fluoro, chloro, bromo, or iodo, to provide the compounds of formula I where R_2 is other than hydroxy or amino; or

(B) heating a compound of the formula

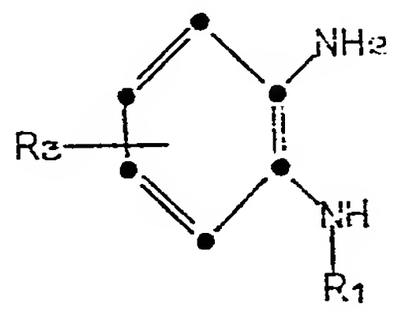


(V)

wherein R_1 and R_3 are defined as above, with formic acid or lactic acid, preferably in the presence of

a mineral acid, to provide the compounds of formula I wherein R_2 is hydrogen or 1-hydroxyethyl; or

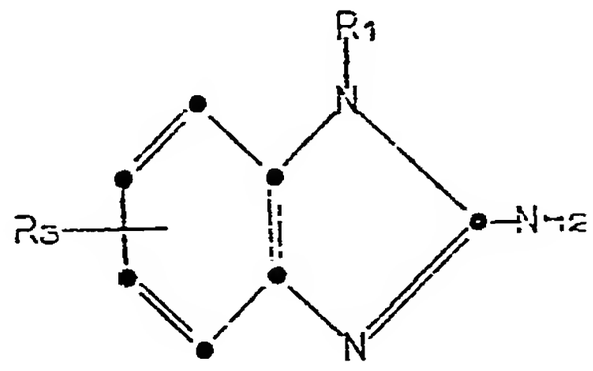
(C) cyclizing a compound of the formula



(V)

wherein R_1 and R_3 are defined as above, with cyanogen halide, to provide the compounds of formula I wherein R_2 is amino; or

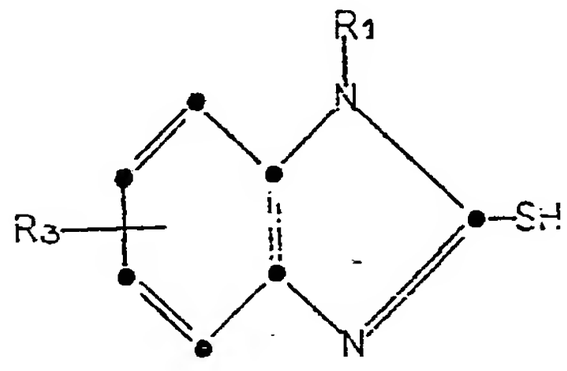
(D) alkylating a benzimidazole compound of the formula



(IB)

wherein R_1 and R_3 are defined as above, with a C_1-C_4 alkyl halide, to provide the compounds of formula I wherein R_2 is C_1-C_4 alkylamino; or

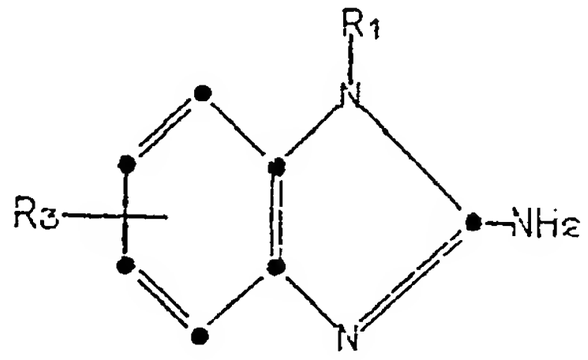
(E) alkylating a benzimidazole compound of the formula



(IC)

wherein R_1 and R_3 are defined as above, with methyl halide in the presence of a weak base, to provide the compounds of formula I wherein R_2 is methylmercapto; or

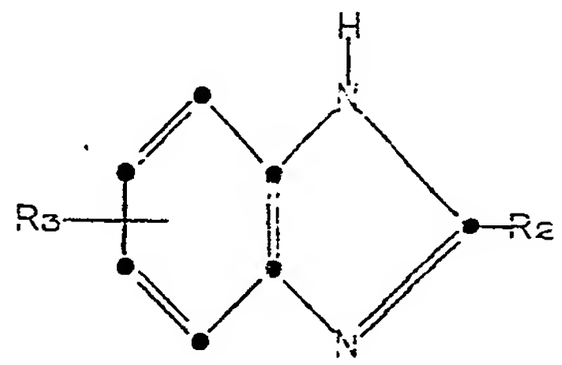
(F) acylating a benzimidazole compound of the formula



(IB)

wherein R_1 and R_3 are defined as above, with a C_2-C_4 anhydride, a mixed anhydride of formic and acetic anhydride, or a C_1-C_4 acyl halide, to provide the compounds of formula I wherein R_2 is C_1-C_4 acylamino; or

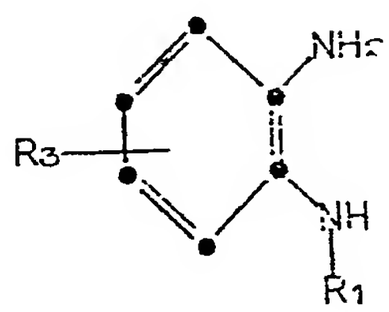
(G) reacting a benzimidazole compound of the formula



(II)

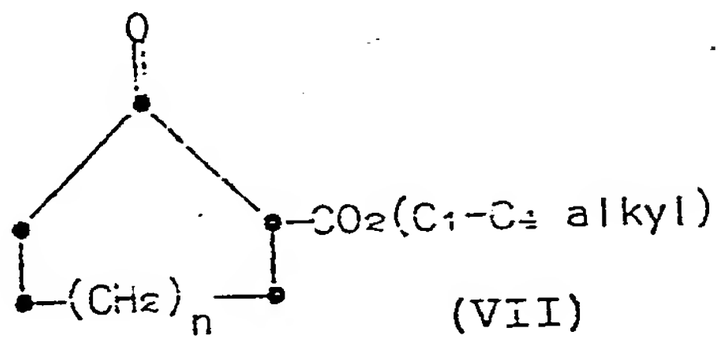
wherein R_2 and R_3 are defined as above, with R_4R_5NH, where R_4 and R_5 are defined as above, and formaldehyde, to provide the compounds of formula I wherein R_1 is $R_4R_5NCH_2$-; or

(H) condensing a compound of the formula



(V)

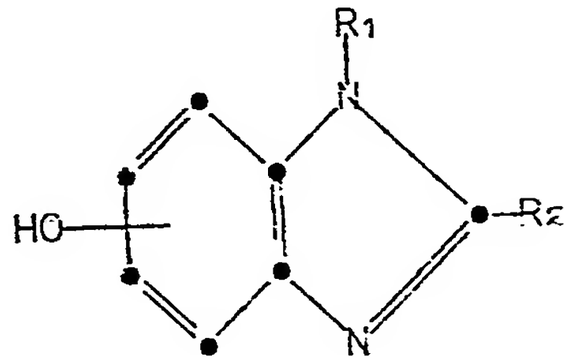
wherein R_1 and R_3 are defined as above, with a β-keto ester of the formula



(VII)

wherein n is 0-2, to provide the compounds of formula I wherein R_2 is hydrogen and R_1 is C_5-C_7 cycloalken-1-yl; or

(I) esterifying a benzimidazole compound of the formula

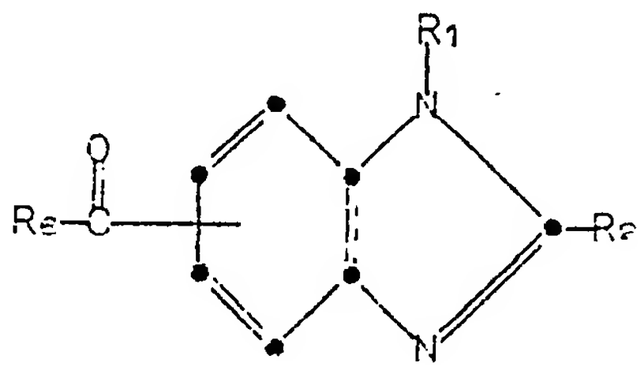


(ID)

wherein R_1 is defined as above, and R_2 does not contain a hydroxy group, with an anhydride or acyl halide, to provide the compounds of formula I wherein R_3

is C_2-C_8 alkanoyloxy, unsubstituted or substituted phenylacetoxy, or unsubstituted or substituted benzoyloxy; or

(J) reacting a benzimidazole compound of the formula



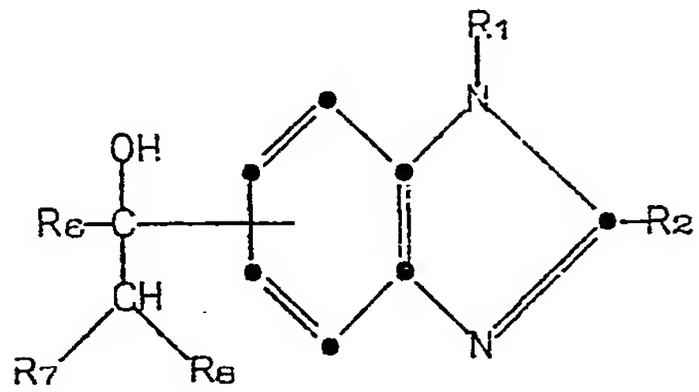
(IA)

wherein R_1, R_2 and R_6 are defined as above, with hydroxylamine, or its hydrochloride salt, hydrazine or C_1-C_4 alkoxyamine, to provide the compounds of formula I wherein Z is hydroxyimino, hydrazono, or C_1-C_4 alkoxyimino; or

(K) acylating a compound of formula I wherein Z is hydroxyimino with a C_1-C_4 anhydride or a C_1-C_4 acyl halide, to provide the compounds of formula I wherein Z is C_1-C_4 acyloxyimino; or

(L) etherifying a compound of formula I wherein Z is hydroxyimino with a C_1-C_4 alkyl halide, or alkylating the compound of formula I where R_3 is R_6-$\overset{O}{\overset{\|}{C}}$- with a C_1-C_4 alkoxyamine, to provide the compounds of formula I wherein Z is C_1-C_4 alkoxyimino; or

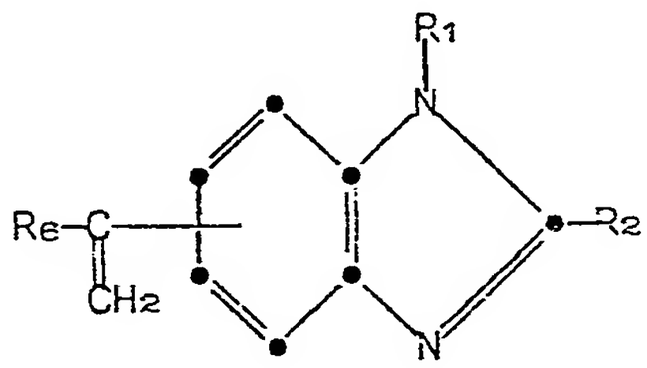
(M) dehydrating a benzimidazole compound of the formula



(IF)

wherein R_1, R_2 and R_6 are defined as above, and one of R_7 and R_8 is hydrogen and the other of R_7 and R_8 is hydrogen, C_1-C_6 alkyl, -CN, $-CONH_2$, or $-CO_2-(C_1-C_4$ alkyl), with an acid, to provide the compounds of formula I wherein Z is C_1-C_7 alkylidene, =CHCN, $=CHCONH_2$, or $=CHCO_2(C_1-C_4$ alkyl); or

(N) reacting a benzimidazole compound of the formula



(IGc)

wherein R_1, R_2 and R_6 are defined as above, with a halogenating agent, to provide the compounds of formula I wherein Z is =CHBr, =CHCl, $=CBr_2$, $=CCl_2$, or =CBrCl; or

(O) resolving the benzimidazole compounds of formula I into its 5 and 6 isomers; or

(P) resolving the benzimidazole compounds of formula I wherein Z is hydroxyimino, C_1-C_4 alkoxyimino, C_1-C_4 acyloxyimino, or hydrazono into its syn and anti isomers; or

(Q) resolving the benzimidazole compounds of formula I wherein Z is C_1-C_7 alkylidene, =CHBr, =CHCl, =CBr_2, =CCl_2, =CBrCl, =CHCN, =$CHCONH_2$ or =$CHCO_2$(C_1-C_4 alkyl) into its cis and trans isomers; or

(R) salifying the compounds of formula I to form pharmaceutically acceptable salts.

2. The process of claim 1 (J) for preparing 1-(t-butyl)-6-(α-hydroxyiminobenzyl)benzimidazole which comprises reacting 1-(t-butyl)-6-benzoylbenzimidazole with hydroxylamine hydrochloride.

3. The process of claim 1 (J) for preparing 1-cyclohexyl-2-amino-6-(α-hydroxyiminobenzyl)benzimidazole which comprises reacting 1-cyclohexyl-2-amino-6-benzoylbenzimidazole with hydroxylamine hydrochloride.

4. The process of claim 1 (J) for preparing 1-cyclohexyl-2-amino-6-(α-hydroxyimino-4'-methoxybenzyl)benzimidazole which comprises reacting 1-cyclohexyl-2-amino-6-(4'-methoxybenzoyl)benzimidazole with hydroxylamine hydrochloride.

5. The process of claim 1 (J) for preparing 1-isopropyl-2-amino-6-(α-hydroxyiminobenzyl)benzimidazole which comprises reacting 1-isopropyl-2-amino-6-benzoylbenzimidazole with hydroxylamine hydrochloride.

6. The process of claim 1 (J) for preparing 1-phenyl-2-amino-6-(α-hydroxyiminobenzyl)benzimidazole which comprises reacting 1-phenyl-2-amino-6-benzoyl-benzimidazole with hydroxylamine hydrochloride.

7. The process of claim 1 (M) for preparing 1-isopropyl-2-amino-6-(1-phenyl-1-propenyl)benzimidazole which comprises reacting 1-isopropyl-2-amino-6-(α-hydroxy-α-ethylbenzyl)benzimidazole with formic acid.

8. The process of claim 1 (N) for preparing 1-isopropyl-2-amino-6-(1-phenyl-2-bromoethenyl)benz-imidazole which comprises reacting 1-isopropyl-2-amino-6-(1-phenylethenyl)benzimidazole with N-bromo-succinimide.

9. The process of claim 1 (M) for preparing 1-isopropyl-2-amino-6-(1-phenyl-2-cyanoethenyl)benz-imidazole which comprises reacting 1-isopropyl-2-amino-6-(α-hydroxy-α-cyanomethylbenzyl)benzimidazole with formic acid.

10. The process of claim 1 (M) for preparing 1-phenyl-2-amino-6-(1-phenyl-2-cyanoethenyl)benzimidazole which comprises reacting 1-phenyl-2-amino-6-(α-hydroxy-α-cyanomethylbenzyl)benzimidazole with formic acid.

11. The process of claim 1 (M) for preparing 3-(1-isopropyl-2-aminobenzimidazol-6-yl)-3-phenyl-2-propenamide which comprises reacting 1-isopropyl-2-amino-6-[α-hydroxy-α-bis(trimethylsilyl)acetamido]-benzylbenzimidazole with ammonium chloride.

12. A benzimidazole of formula I or a pharmaceutically acceptable salt thereof, whenever prepared by a process according to any one of claims 1-11.